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<p>(21) International Application Number: PCT/GB89/01398</p> <p>(22) International Filing Date: 23 November 1989 (23.11.89)</p> <p>(30) Priority data: 8827308.1 23 November 1988 (23.11.88) GB</p> <p>(71) Applicant (for all designated States except US): BRITISH BIO-TECHNOLOGY LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : DAVIDSON, Alan, Hornsby [GB/GB]; 27 Newland Mill, Witney, Oxon OX8 6HH (GB). DICKENS, Jonathan, Philip [GB/GB]; Burton House, Park Farm Road, High Wycombe, Bucks HP12 4AF (GB). CRIMMIN, Michael, John [GB/GB]; Oaklea, 64 Fernbank Road, Ascot SL5 8HE (GB).</p>		<p>(74) Agents: SHEARD, Andrew, Gregory et al.; Kilburn & Strode, 30 John Street, London WC1N 2DD (GB).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, ES (European patent), FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS</p> <div style="text-align: center; margin: 20px 0;"> <p style="text-align: right;">(I)</p> </div> <div style="text-align: center; margin: 20px 0;"> <p style="text-align: right;">α</p> </div> <p>(57) Abstract</p> <p>Compounds of general formula (I), wherein R₁ represents a hydrogen atom or a C₁-C₆ alkyl, C₁-C₆ alkenyl, phenyl, phenyl(C₁-C₆)alkyl, C₁-C₆ alkylthiomethyl, phenylthiomethyl, substituted phenylthiomethyl, phenyl(C₁-C₆)alkylthiomethyl or heterocyclylthiomethyl group; or R₁ represents -SR^x wherein R^x represents a group (α); R₂ represents a hydrogen atom or a C₁-C₆ alkyl, C₁-C₆ alkenyl, phenyl(C₁-C₆)alkyl, cycloalkyl(C₁-C₆)alkyl, or cycloalkenyl(C₁-C₆)alkyl; R₃ represents an amino acid residue with R or S stereochemistry or a C₁-C₆ alkyl, benzyl, (C₁-C₆)alkoxybenzyl or benzyloxy(C₁-C₆)alkyl group; R₄ represents a hydrogen atom or a methyl group; n is an integer from 1 to 6; and A represents the group -NH₂, a substituted acyclic amine or a heterocyclic base; or a salt and/or N-oxide and/or (where the compound is a thio-compound) a sulfoxide or sulphone thereof have collagenase inhibition activity and are useful in the management of disease involving tissue degradation and/or the promotion of wound healing. Diseases involving tissue degradation include arthropathy (particularly rheumatoid arthritis), inflammation, dermatological diseases, bone resorption diseases and tumour invasion.</p>		

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1 HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS

2

3 This invention relates to pharmaceutically and
4 veterinarily active compounds, which are derivatives of
5 hydroxamic acid.

6

7 The compounds of the present invention act as
8 inhibitors of metalloproteases involved in tissue
9 degradation, such as collagenase, which initiates
10 collagen breakdown, stromelysin (proteoglycanase),
11 gelatinase and collagenase (IV). There is evidence
12 implicating collagenase as one of the key enzymes in
13 the breakdown of articular cartilage and bone in
14 rheumatoid arthritis (Arthritis and Rheumatism, 20,
15 1231 - 1239, 1977). Potent inhibitors of collagenase
16 and other metalloproteases involved in tissue
17 degradation are useful in the treatment of rheumatoid
18 arthritis and related diseases in which collagenolytic
19 activity is important. Inhibitors of metalloproteases
20 of this type can therefore be used in treating or
21 preventing conditions which involve tissue breakdown;
22 they are therefore useful in the treatment of
23 arthropathy, dermatological conditions, bone
24 resorption, inflammatory diseases and tumour invasion
25 and in the promotion of wound healing. Specifically,
26 compounds of the present invention may be useful in the
27 treatment of osteopenias such as osteoporosis,
28 rheumatoid arthritis, osteoarthritis, periodontitis,
29 gingivitis, corneal ulceration and tumour invasion.

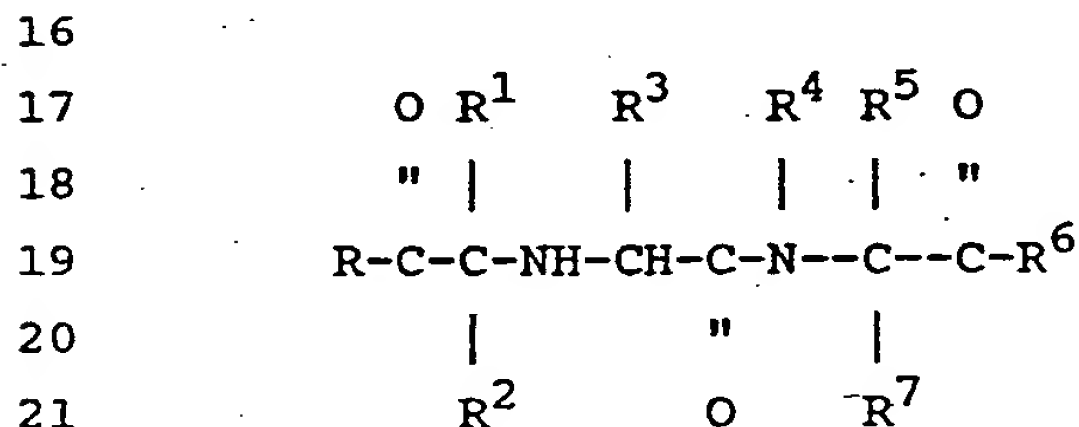
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31 A number of small peptide like compounds which
32 inhibit metalloproteases have been described. Perhaps
33 the most notable of these are those relating to the

1 angiotensin converting enzyme (ACE) where such
 2 agents act to block the conversion of the decapeptide
 3 angiotensin I to angiotensin II a potent pressor
 4 substance. Compounds of this type are described in
 5 EP-A-0012401.

6
 7 Certain hydroxamic acids have been suggested as
 8 collagenase inhibitors as in US-A-4599361 and
 9 EP-A-0236872. Other hydroxamic acids have been prepared
 10 as ACE inhibitors, for example in US-A-4105789, while
 11 still others have been described as enkephalinase
 12 inhibitors as in US-A-4496540.

13
 14 EP-A-0012401 discloses antihypertensive compounds of
 15 the formula:



20
 21
 22
 23 wherein

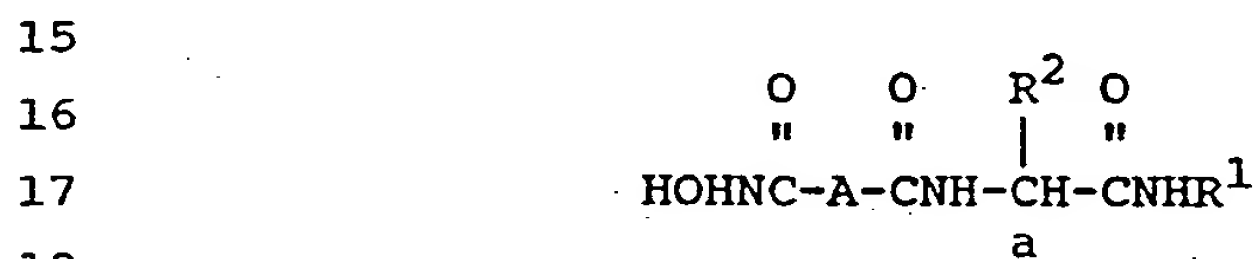
24
 25 R and R⁶ are the same or different and are hydroxy,
 26 alkoxy, alkenoxy, dialkylamino alkoxy, acylamino
 27 alkoxy, acyloxy alkoxy, aryloxy, alkyloxy, substituted
 28 aryloxy or substituted aralkoxy wherein the substituent
 29 is methyl, halo, or methoxy, amino, alkylamino,
 30 dialkylamino, aralkylamino or hydroxyamino;

- 1 R^1 is hydrogen, alkyl of from 1 to 20 carbon atoms,
2 including branched, cyclic and unsaturated alkyl
3 groups;
4
5 substituted alkyl wherein the substituent is halo,
6 hydroxy, alkoxy, aryloxy amino, alkylamino,
7 dialkylamino, acrylamino, arylamino, guanidino,
8 imidazolyl, indolyl, mercapto, alkylthio, arylthio,
9 carboxy, carboxamido, carbalkoxy, phenyl, substituted
10 phenyl wherein the substituent is alkyl, alkoxy or
11 halo; aralkyl or heteroaralkyl, aralkenyl or
12 heteroaralkenyl, substituted aralkyl, substituted
13 heteroaralkyl, substituted aralkenyl or substituted
14 heteroaralkenyl, wherein the substituent is halor or
15 dihalo, alkyl, hydroxy, alkoxy, amino, aminomethyl,
16 acrylamino, dialkylamino, alkylamino, carboxyl,
17 haloalkyl, cyano or sulphonamido, aralkyl or
18 heteroaralkyl substituted on the alkyl portion by
19 amino or acylamino;
20
21 R^2 and R^7 are hydrogen or alkyl;
22
23 R^3 is hydrogen, alkyl, phenylalkyl,
24 aminomethylphenylalkyl, hydroxyphenylalkyl,
25 hydroxyalkyl, acetylaminoalkyl, acylaminoalkyl,
26 acylaminoalkyl aminoalkyl, dimethylaminoalkyl,
27 haloalkyl, guanidinoalkyl, imidazolylalkyl,
28 indolylalkyl, mercaptoalkyl and alkylthioalkyl;
29
30 R^4 is hydrogen or alkyl;
31
32
33

1 R^5 is hydrogen, alkyl, phenyl, phenylalkyl,
 2 hydroxyphenylalkyl, hydroxyalkyl, aminoalkyl,
 3 guanidinoalkyl, imidazolylalkyl, indolylalkyl,
 4 mercaptoalkyl or alkylthioalkyl;

5
 6 R^4 and R^5 may be connected together to form an alkylene
 7 bridge of from 2 to 4 carbon atoms, an alkylene bridge
 8 of from 2 to 3 carbon atoms and one sulphur atom, an
 9 alkylene bridge of from 3 to 4 carbon atoms containing
 10 a double bond or an alkylene bridge as above,
 11 substituted with hydroxy, alkoxy or alkyl and the
 12 pharmaceutically acceptable salts thereof.

13
 14 US-A-4599361 discloses compounds of the formula:



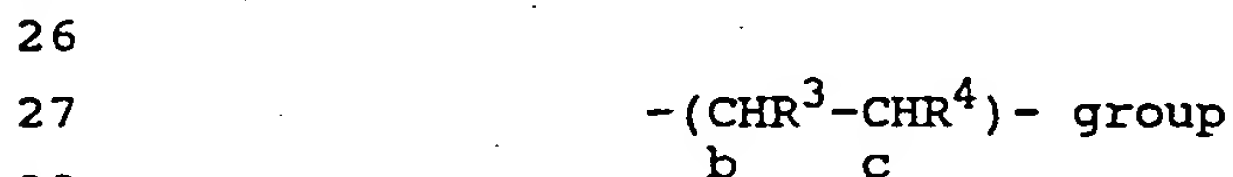
18
 19 wherein

20 R^1 is C_1-C_6 alkyl;

21 R^2 is C_1-C_6 alkyl, benzyl, benzyloxybenzyl, (C_1-C_6
 22 alkoxy)benzyl or benzyloxy(C_1-C_6 alkyl);

23 a is a chiral centre with optional R or S
 24 stereochemistry;

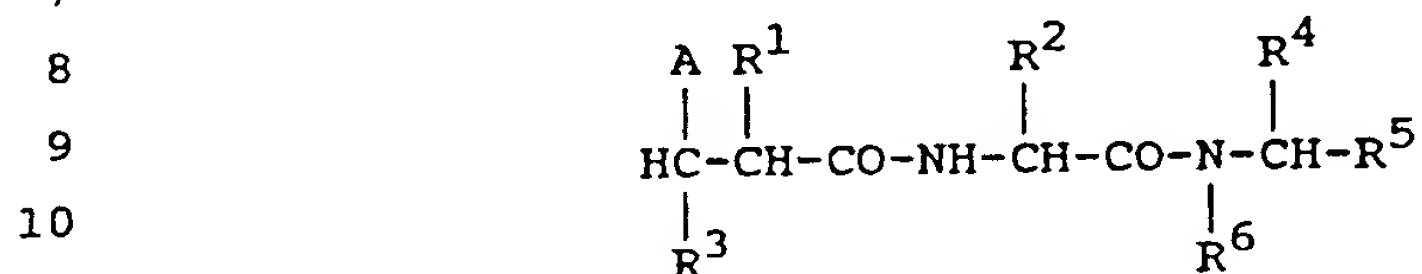
25 A is a



29 or a $-(CR^3=CR^4)-$ group wherein b and c are chiral
 30 centres with optional R or S stereochemistry;
 31
 32
 33

1 R^3 is hydrogen, C_1-C_6 alkyl, phenyl or phenyl(C_1-C_6
 2 alkyl) and R^4 is hydrogen, C_1-C_6 alkyl, phenyl(C_1-C_6
 3 alkyl), cycloalkyl or cycloalkyl(C_1-C_6 alkyl).

4
 5 EP-A-0236872 discloses generically compounds of the
 6 formula



12 wherein

14 A represents a group of the formula $HN(OH)-CO-$ or
 15 $HCO-N(OH)-$;

17 R^1 represents a C_2-C_5 alkyl group;

19 R^2 represents the characterising group of a natural
 20 alpha-amino acid in which the functional group can be
 21 protected, amino groups may be acylated and carboxyl
 22 groups can be amidated, with the proviso that R^2 can
 23 not represent hydrogen or a methyl group;

25 R^3 represents hydrogen or an amino, hydroxy, mercapto,
 26 C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acylamino,
 27 C_1-C_6 -alkylthio, aryl-(C_1-C_6 alkyl)-,
 28 amino-(C_1-C_6 -alkyl)-, hydroxy(C_1-C_6 -alkyl)-,
 29 mercapto(C_1-C_6 alkyl) or carboxy(C_1-C_6 alkyl) group,
 30 wherein the amino, hydroxy, mercapto or carboxyl groups
 31 can be protected and the amino groups may be acylated
 32 or the carboxyl groups may be amidated;

1 R^4 represents hydrogen or a methyl group;

2

3 R^5 represents hydrogen or a C_1-C_6 acyl, C_1-C_6
4 alkoxy- C_1-C_6 alkyl, di(C_1-C_6 -alkoxy)methylene, carboxy,
5 (C_1-C_6 alkyl)carbiny, (C_1-C_6 alkoxy)carbiny,
6 arylmethoxy carbiny, (C_1-C_6 alkyl)amino carbiny or
7 arylamino carbiny group; and

8

9 R^6 represents hydroxy or a methylene group; or

10

11 R^2 and R^4 together represent a group- $(CH_2)_n$ -, wherein n
12 represents a number from 4 to 11; or

13

14 R^4 and R^5 together represent a trimethylene group;

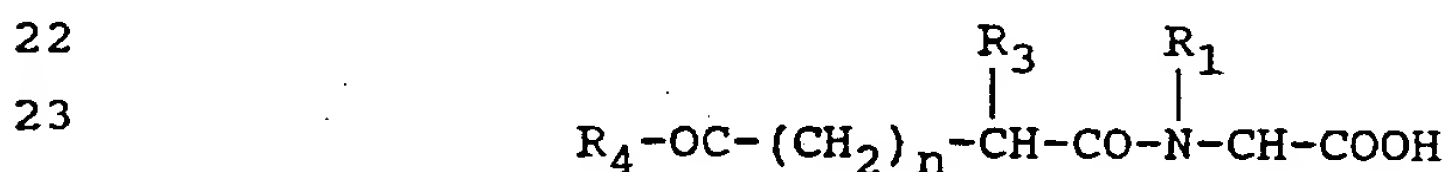
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16 and pharmaceutically acceptable salts of such
17 compounds, which are acid or basic.

18

19 US-A-4105789 generically discloses compounds which have
20 the general formula

21



24

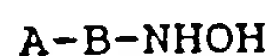
25 and salts thereof, wherein

26

27 R_1 is hydrogen, lower alkyl, phenyl lower alkylene,
28 hydroxy-lower alkylene, hydroxyphenyl lower
29 alkylene, amino-lower alkylene, guanidine lower
30 alkylene, mercapto-lower alkylene, lower
31 alkyl-mercapto-lower alkylene, imidazolyl lower
32 alkylene, indolyl-lower alkylene or carbamoyl
33 lower alkylene;

- 1 R_2 is hydrogen or lower alkyl;
 2 R_3 is lower alkyl or phenyl lower alkylene;
 3 R_4 is hydroxy, lower alkoxy or hydroxyamino; and
 4 n is 1 or 2.

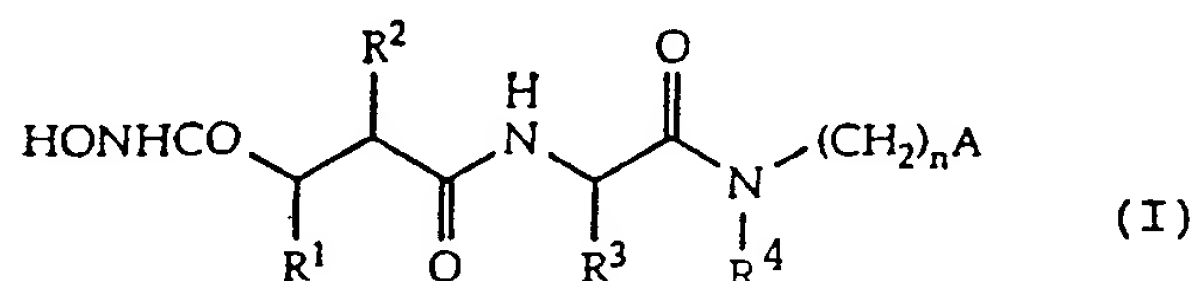
5
 6 US-A-4496540 discloses compounds of the general
 7 formula:



10
 11 wherein A is one of the aromatic group-containing amino
 12 acid residues L-tryptophyl, D-tryptophyl, L-tyrosyl,
 13 D-tyrosyl, L-phenylalanyl, or D-phenylalanyl, and B is
 14 one of the amino acids glycine, L-alanine, D-alanine,
 15 L-leucine, D-leucine, L-isoleucine, or D-isoleucine;
 16 and pharmaceutically acceptable salts thereof.

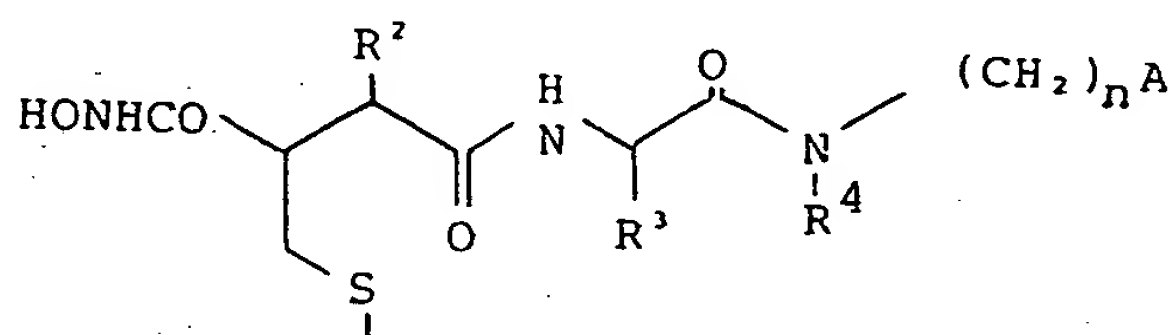
17
 18 It would be desirable to improve on the solubility of
 19 known collagenase inhibitors and/or stromelysin
 20 inhibitors (whether as the free base or the salt) and,
 21 furthermore, increases in activity have also been
 22 sought. It is not a simple matter, however, to predict
 23 what variations in known compounds would be desirable
 24 to increase or even retain activity; certain
 25 modifications of known hydroxamic acid derivatives have
 26 been found to lead to loss of activity.

27
 28 According to a first aspect of the invention, there is
 29 provided a compound of general formula I:



1 wherein:

2
 3 R^1 represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6
 4 alkenyl, phenyl, phenyl(C_1-C_6)alkyl, C_1-C_6
 5 alkylthiomethyl, phenylthiomethyl, substituted
 6 phenylthiomethyl, phenyl(C_1-C_6)alkylthiomethyl or
 7 heterocyclylthiomethyl group; or R^1 represents
 8 $-SR^X$ wherein R^X represents a group



17 R^2 represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6
 18 alkenyl, phenyl(C_1-C_6)alkyl,
 19 cycloalkyl(C_1-C_6)alkyl, or
 20 cycloalkenyl(C_1-C_6)alkyl;

21
 22 R^3 represents an amino acid side chain or a C_1-C_6
 23 alkyl, benzyl, (C_1-C_6)alkoxybenzyl,
 24 benzyloxy(C_1-C_6)alkyl or benzyloxybenzyl group;

25
 26 R^4 represents a hydrogen atom or a methyl group;

27
 28 n is an integer from 1 to 6; and

29
 30 A represents the group $-NH_2$, a substituted acyclic
 31 amine or a heterocyclic base;

32

33

1 or a salt and/or N-oxide and/or (where the compound is
2 a thio-compound) a sulfoxide or sulphone thereof.

3

4 Hereafter in this specification, the term "compound"
5 includes "salt" unless the context requires otherwise.

6

7 As used herein the term " C_1 - C_6 alkyl" refers to a
8 straight or branched chain alkyl moiety having from
9 one to six carbon atoms, including for example,
10 methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl,
11 pentyl and hexyl, and cognate terms (such as " C_1 - C_6
12 alkoxy") are to be construed accordingly.

13

14 The term " C_1 - C_6 alkenyl" refers to a straight or
15 branched chain alkyl moiety having one to six carbons
16 and having in addition one double bond, of either E or
17 Z stereochemistry where applicable. This term would
18 include, for example, an alpha, beta-unsaturated
19 methylene, vinyl, 1-propenyl, 1- and 2-butenyl and
20 2-methyl-2-propenyl.

21

22 The term "cycloalkyl" refers to a saturated
23 alicyclic moiety having from 3 to 8 carbon atoms
24 and includes, for example, cyclopropyl, cyclobutyl,
25 cyclopentyl and cyclohexyl.

26

27 The term "cycloalkenyl" refers to an unsaturated
28 alicyclic moiety having from 3 to 8 carbon atoms
29 and includes, for example, cyclopropenyl, cyclobutenyl,
30 cyclopentenyl and cyclohexenyl.

31

32

33

1 The term "substituted acyclic amine" refers to a group
2 $-N(R^A)R^B$, wherein each of R^A and R^B independently
3 represents a hydrogen atom or a C_1-C_6 alkyl group, with
4 the proviso that at least one of R^A and R^B represents a
5 C_1-C_6 alkyl group.

6

7 The term "heterocyclic base" refers to a group of
8 general formula (II):

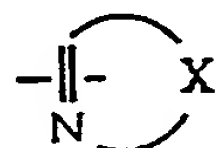
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(II)

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which represents a five or six membered saturated or
unsaturated ring with or without an extra heteroatom
(such as nitrogen and/or sulphur and/or oxygen) which
may be fused to a benzene ring, for example pyridyl,
imidazolyl, oxazolyl, thiazolyl, benzthiazolyl,
benzoxazolyl, morpholinyl, pyrrolidinyl or piperidinyl.
Preferred heterocyclic bases include pridyl,
morpholinyl, piperidinyl and pyrrolidinyl.

The term "heterocyclylthiomethyl" refers to a
methyl group substituted by a hetrocyclic thiol for
example pyridine-2-thiol, pyridine-4-thiol,
thiophene-2-thiol or pyrimidine-2-thiol.

The term "substituted", as applied to a phenyl or other
aromatic ring, means substituted with up to four
substituents each of which independently may be C_1-C_6
alkyl, C_1-C_6 alkoxy, hydroxy, thiol, C_1-C_6 alkylthiol
amino, halo (including fluoro, chloro, bromo and iodo),
triflouromethyl or nitro.

1 The term "amino acid side chain" means a characteristic
2 side chain attached to the $-\text{CH}(\text{NH}_2)(\text{COOH})$ moiety in the
3 following R or S amino acids: glycine, alanine, valine,
4 leucine, isoleucine, phenylalanine, tyrosine,
5 tryptophan, serine, threonine, cysteine, methionine,
6 asparagine, glutamine, lysine, histidine, arginine,
7 glutamic acid and aspartic acid.

8
9 There are several chiral centres in the compounds
10 according to the invention because of the presence of
11 asymmetric carbon atoms. The presence of several
12 asymmetric carbon atoms gives rise to a number of
13 diastereomers with the appropriate R or S
14 stereochemistry at each chiral centre. General formula
15 I and, where appropriate, all other formulae in this
16 specification are to be understood to include all such
17 stereoisomers and mixtures (for example racemic
18 mixtures) thereof. Compounds in which the chiral centre
19 adjacent the substituent R^3 has S stereochemistry are
20 preferred.

21
22 Further or other preferred compounds include those in
23 which, independently or in any combination:

24
25 R^1 represents a hydrogen atom or a C_1 - C_4 alkyl (such
26 as methyl), phenylthiomethyl or
27 heterocyclylthiomethyl (such as
28 thiophenylthiomethyl) group;

29 R^2 represents a C_3 - C_6 alkyl (such as isobutyl or
30 n-pentyl) group;

31 R^3 represents a benzyl, 4- $(\text{C}_1$ - $\text{C}_6)$ alkoxyphenylmethyl
32 or benzyloxy benzyl group;

33 R^4 represents a hydrogen atom;

1 n has the value 1, 2 or 3; and/or
2 A represents a morpholinyl (eg 4-morpholinyl),
3 piperidinyl, 2-, 3- or 4-pyridyl or pyrrolidinyl
4 group.

5

6 Particularly preferred compounds include:

7

- 8 1. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
9 alanine-N-[(2-aminoethyl)-2(RS)-(1-methyl-
10 pyrrolidine)]amide,
11
- 12 2. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
13 alanine-N-[1-(2-aminoethyl)-piperidine]amide,
14
- 15 3. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
16 alanine-N-[1-(2-aminoethyl)-pyrrolidine]amide,
17
- 18 4. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
19 alanine-N-[1-(3-aminopropyl)-2(RS)-methyl-
20 piperidine]amide,
21
- 22 5. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
23 alanine-N-[2-(2-aminoethyl)-1-methylpyrrole]amide,
24
- 25 6. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
26 alanine-N-(3-aminomethylpyridine)amide,
27
- 28 7. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
29 alanine-N-(2-aminomethylpyridine)amide,
30
- 31 8. [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-
32 phenylalanine-N-(4-aminomethylpyridine)amide,
33

- 1 9. [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-
2 phenylalanine-N-(1-(3-aminopropyl)-imidazole)amide,
3
4 10. [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-
5 phenylalanine-N-(2-aminomethylbenzimidazole)amide,
6
7 11. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
8 succinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-
9 morpholino]amide,
10
11 12. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
12 alanine-N-[4-(2-aminoethyl)-morpholine]amide,
13
14 13. [4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-
15 phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide,
16
17 14. [4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-
18 phenylalanine-N-[4-(2-aminopropyl)-morpholine]-
19 amide,
20
21 15. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
22 alanine-N-(3-aminomethylpyridine)amide hydro-
23 chloride,
24
25 16. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
26 phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide
27 hydrochloride,
28
29 17. [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-
30 phenylalanine-N-(4-aminomethylpyridine)amide
31 hydrochloride,
32
33

- 1 18. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
2 succinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-
3 morpholine]amide hydrochloride and
4
- 5 19. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
6 succinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-
7 morpholine]amide sodium salt,
8
- 9 20. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
10 alanine-N-[1-(3-aminopropyl)-imidazole]amide
11
- 12 21. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
13 alanine-N-[2-(3-aminopropyl)-pyridine]amide
14
- 15 22. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
16 alanine-N-[2-aminoethyl)-N,N-diethylamine]amide
17
- 18 23. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
19 succinyl]-l-phenylalanine-N-[3-aminomethyl-
20 pyridine]amide
21
- 22 24. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
23 succinyl]-l-phenylalanine-N-[4-aminomethyl-
24 pyridine]amide
25
- 26 25. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
27 succinyl]-l-phenylalanine-N-[2-aminomethyl-
28 pyridine]amide
29
- 30 26. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
31 succinyl]-l-phenylalanine-N-[2-(2-aminoethyl)-
32 pyridine]amide
33

- 1 27. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
2 alanine-N-[2-(2-aminoethyl)-pyridine]amide hydro-
3 chloride
4
- 5 28. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
6 alanine-N-[4-aminomethyl-pyridine]amide
7 hydrochloride
8
- 9 29. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
10 alanine-N-[2-aminomethyl-pyridine]amide hydro-
11 chloride
12
- 13 30. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
14 alanine-N-[2-(3-aminopropyl)-pyridine]amide hydro-
15 chloride
16
- 17 31. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
18 succinyl]-l-phenylalanine-N-[3-aminomethyl-
19 pyridine]amide hydrochloride
20
- 21 32. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
22 succinyl]-l-phenylalanine-N-[2-(2-aminoethyl)-
23 pyridine]amide hydrochloride
24
- 25 33. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
26 succinyl]-l-phenylalanine-N-[2-aminomethyl-
27 pyridine]amide hydrochloride
28
- 29 34. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
30 succinyl]-l-phenylalanine-N-[4-aminomethyl-
31 pyridine]amide sodium salt
32
33

- 1 35. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
2 succinyl]-1-phenylalanine-N-[2-(2-aminoethyl)-
3 pyridine]amide sodium salt
4
- 5 36. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
6 succinyl]-1-phenylalanine-N-[3-aminomethyl-
7 pyridine]amide sodium salt
8
- 9 37. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-1-phenyl-
10 alanine-N-[2-(3-aminopropyl)-pyridine]amide sodium
11 salt
12
- 13 38. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-
14 methyl)succinyl]-L-phenylalanine-N-(2-methyl-
15 pyridyl) amide
16

17 and the free bases, free acids and salts thereof, where
18 appropriate. Compounds 6 and 11 are especially
19 preferred because of their good collagenase-inhibiting
20 and protoglycanase inhibiting activities and compound 6
21 is the most preferred.

22

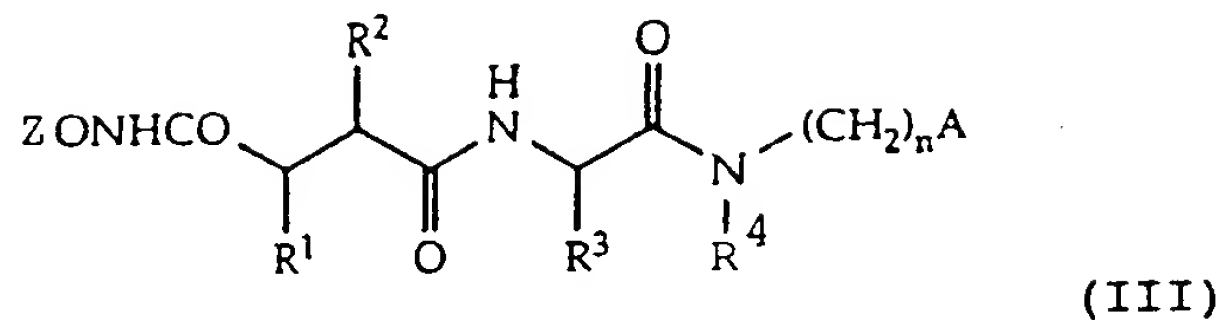
23 Compounds of general formula I may be prepared by any
24 suitable method known in the art and/or by the
25 following process, which itself forms part of the
26 invention.

27

28 According to a second aspect of the invention, there is
29 provided a process for preparing a compound of general
30 formula I as defined above, the process comprising:

31

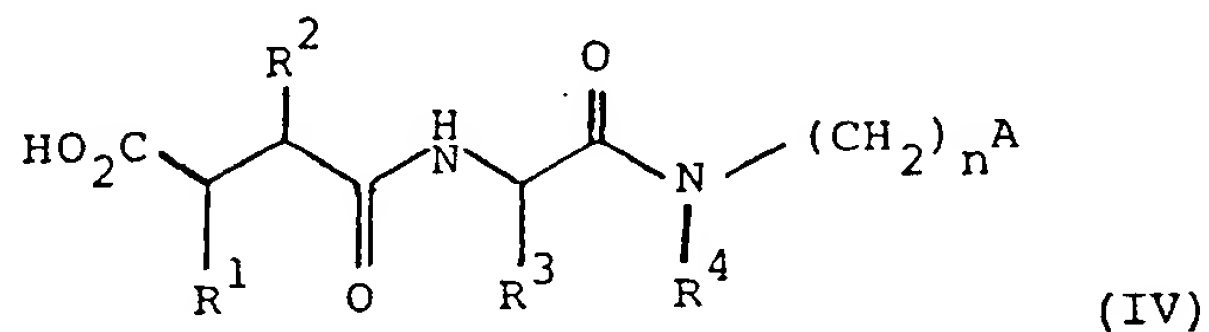
32 (a) deprotecting (for example by hydrogenating) a
33 compound of general formula III



wherein:

R^1 , R^2 , R^3 , R^4 , n and A are as defined in general formula I and Z represents a protective group, such as a benzyl group; or

(b) reacting a compound of general formula IV



wherein:

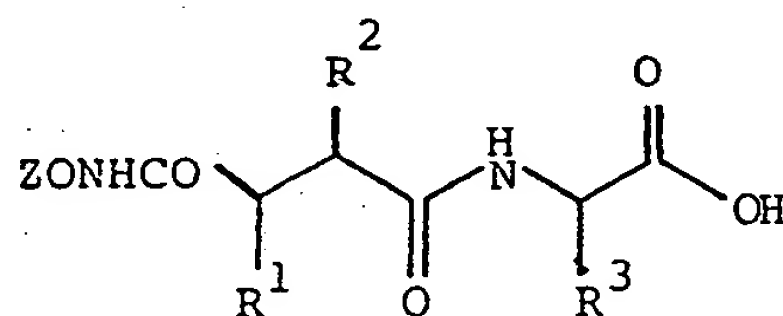
R^1 , R^2 , R^3 , R^4 , n and A are as defined in general formula I, with the proviso that R^1 represents a hydrogen atom,

with hydroxylamine or a salt thereof; and

(c) optionally after step (a) or step (b) converting a compound of general formula I into another compound of general formula I.

1 Compounds of general formula I which are sulphoxides or
 2 sulphones can be derived from thiol compounds of
 3 general formula I by oxidation. Alternatively, thiols
 4 of general formula III or IV can be oxidised.
 5 Compounds of general formula I which are disulphides
 6 (ie compounds wherein R^1 represents SR^X) may be derived
 7 from thiol compounds of general formula I by mild
 8 oxidation with, for example, iodine in methanol.

9
 10 A compound of general formula III can be obtained by
 11 coupling, for example by conventional coupling
 12 techniques, a compound of general formula IV with an
 13 O-protected (for example benzyl) hydroxylamine or by
 14 reacting a compound of general formula V

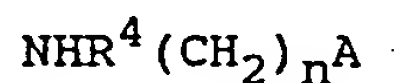


(V)

21
 22 wherein:

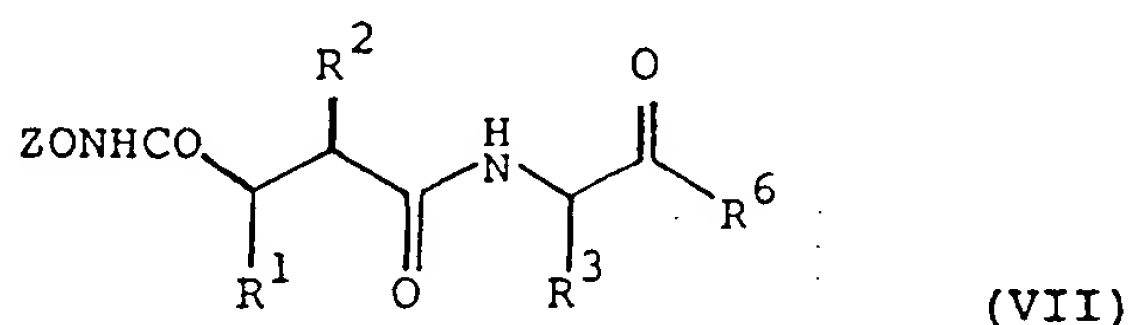
23
 24 R^1 , R^2 and R^3 are as defined in general formula I
 25 and Z represents a protective group such as
 26 benzyl,

27
 28 with a compound of general formula VI



(VI)

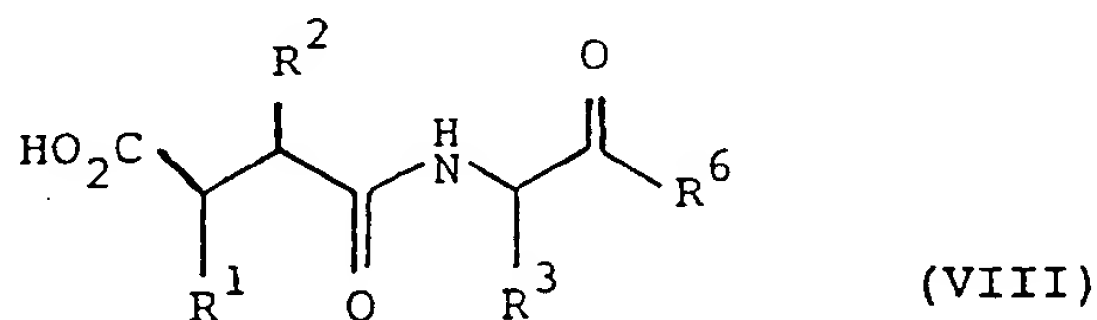
1 A compound of general formula V may be prepared by
 2 hydrolysis in the presence of a base such as sodium
 3 hydroxide of a compound of general formula VII



10
 11 wherein:

12
 13 R^1 , R^2 and R^3 are as defined in general formula I,
 14 with the proviso that R^1 represents a hydrogen
 15 atom, R^6 represents a C_1 - C_6 alkoxy, benzyloxy or
 16 substituted (eg 4-nitro) benzyloxy group, and Z
 17 represents a protective group.

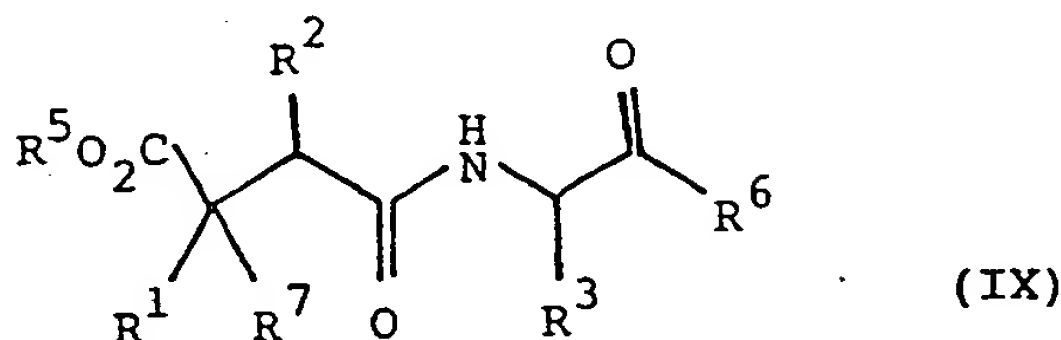
18
 19 A compound of general formula VII may be prepared by
 20 coupling, for example by conventional coupling
 21 techniques, a compound of general formula VIII with an
 22 O-protected (for example benzyl) hydroxylamine



28
 29 wherein:

30
 31 R^1 , R^2 and R^3 are as defined in general formula I
 32 and R^6 represents a C_1 - C_6 alkoxy, benzyloxy or
 33 substituted benzyloxy group.

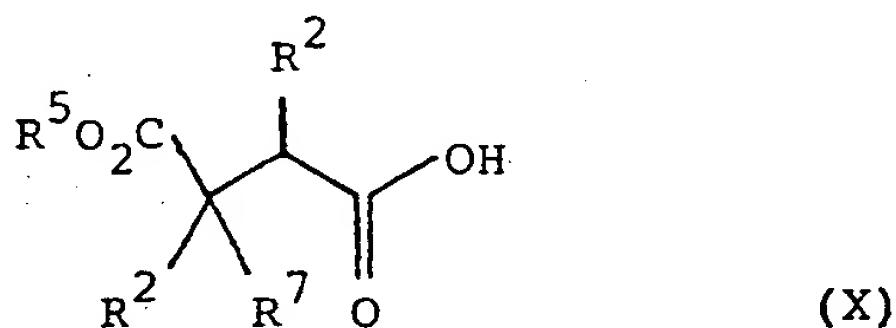
1 A compound of general formula VIII may be prepared by
 2 hydrogenating and (eg thermally) decarboxylating a
 3 compound of general formula IX



10 wherein:

11
 12 R^1 , R^2 and R^3 are as defined in general formula I,
 13 R^5 represents a C_1 - C_6 alkyl or benzyl group, R^6
 14 represents a C_1 - C_6 alkoxy, benzyloxy or
 15 substituted benzyloxy group and R^7 represents a
 16 C_1 - C_6 alkoxycarbonyl or benzyloxycarbonyl group.

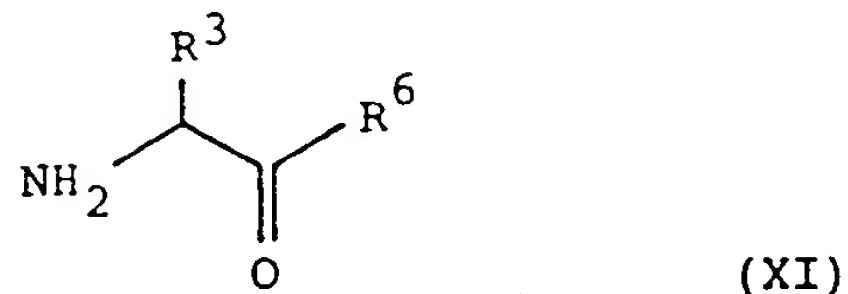
17
 18 A compound of general formula IX may be prepared by
 19 reacting a substituted acid of general formula X



26 wherein:

27
 28 R^1 and R^2 are as defined in general formula I, R^5
 29 represents a C_1 - C_6 alkyl or benzyl group and R^7
 30 represents a C_1 - C_6 alkoxycarbonyl or
 31 benzyloxycarbonyl group, with

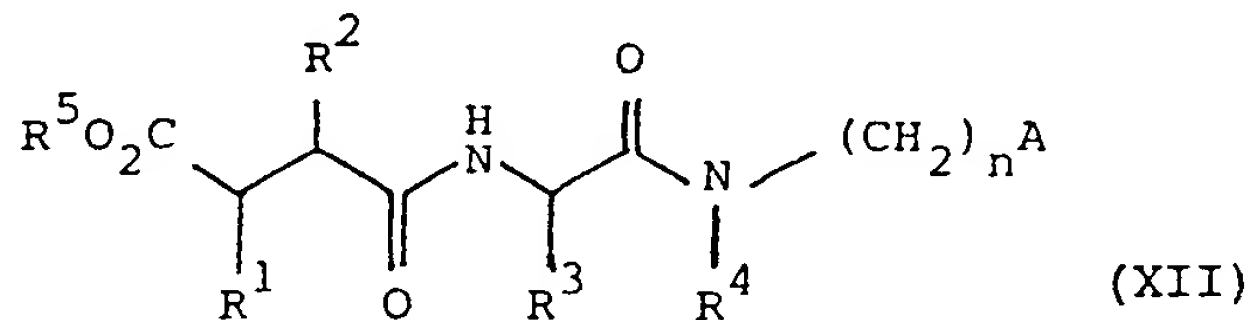
1 an amino acid derivative of general formula (XI)



8 wherein:

10 R^3 is as defined in general formula I and R^6
 11 represents a $\text{C}_1\text{-C}_6$ alkoxy, benzyloxy or
 12 substituted benzyloxy group.

14 Alternatively, a compound of general formula IV can be
 15 prepared by de-esterifying (for example hydrolysing,
 16 under acid or base catalysis) a compound of general
 17 formula XII

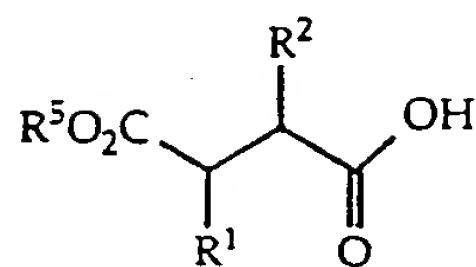


24 wherein:

26 R^1 , R^2 , R^3 , R^4 , n and A are as defined in general
 27 formula I and R^5 represents a $\text{C}_1\text{-C}_6$ alkyl or
 28 benzyl group.

30 A compound of general formula XII can be prepared in a
 31 manner analogous to the preparation of a compound of
 32 formula IX by reacting a substituted acid of general
 33 formula XIII

22

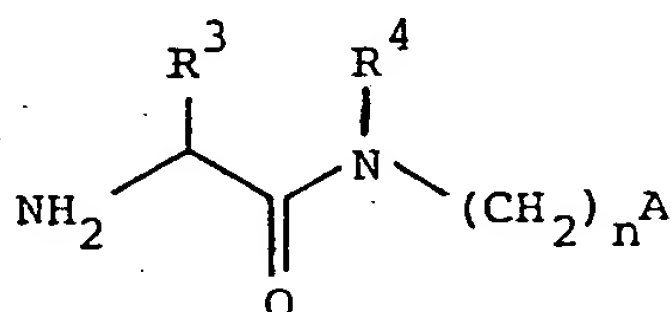


(XIII)

wherein:

R^1 and R^2 are as defined in general formula I and
 R_5 represents a C_1 - C_6 alkyl or benzyl group,

with an amino acid derivative of general formula XIV

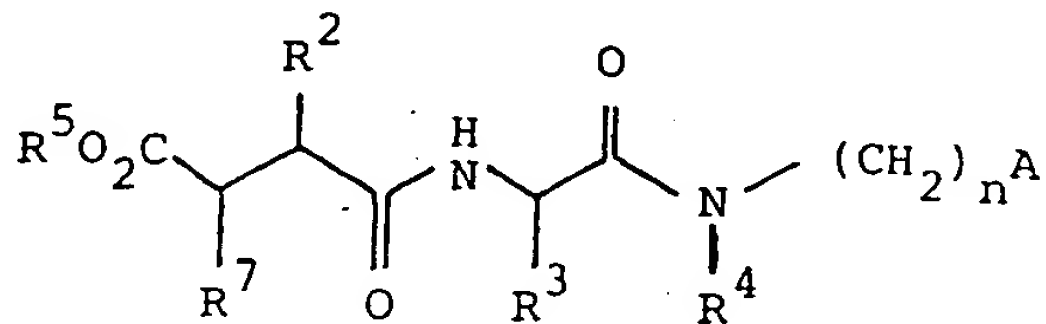


(XIV)

wherein:

R^3 , R^4 , n and A are as defined in general formula I.

In a further synthetic variant, a compound of general formula X as defined above wherein R^1 represents a hydrogen atom can be reacted with a compound of general formula XIV to produce a compound of general formula XV

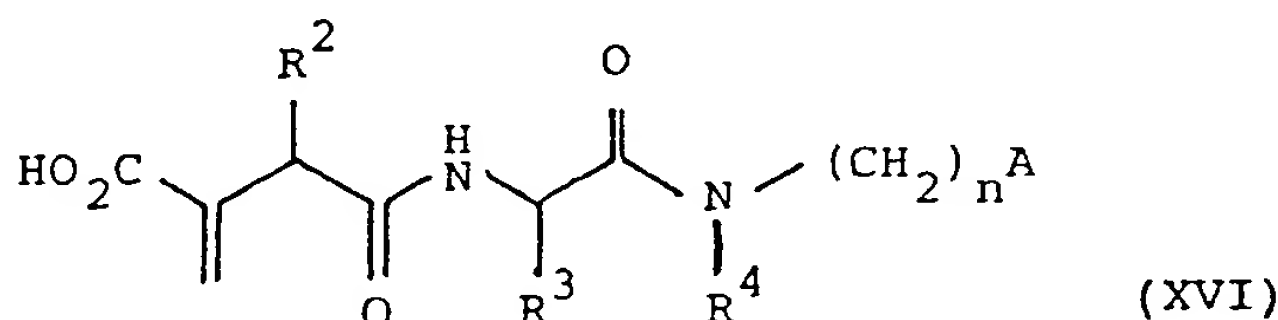


(XV)

wherein:

1 R^2 , R^3 , R^4 , n and A are as defined in general
 2 formula I, R^5 represents a C_1 - C_6 alkyl or benzyl
 3 group and R^7 represents a C_1 - C_6 alkoxy carbonyl or
 4 benzyloxycarbonyl group.

5
 6 A compound of general formula XV wherein R^5
 7 represents benzyl and R^1 represents benzyloxycarbonyl
 8 may be hydrogenated to the malonic acid, then treatment
 9 with aqueous formaldehyde and piperidine gives a
 10 compound of formula XVI



17 wherein:

18
 19 R^2 , R^3 , R^4 , n and A are as defined in general
 20 formula I.

21
 22 Compounds of general formula XVI, by treatment with the
 23 appropriate thiols give the acids of general formula IV
 24 where R^1 is a substituted thiomethyl derivative.
 25 Thiomethyl derivatives can be oxidised to sulfoxides
 26 and sulphones as appropriate.

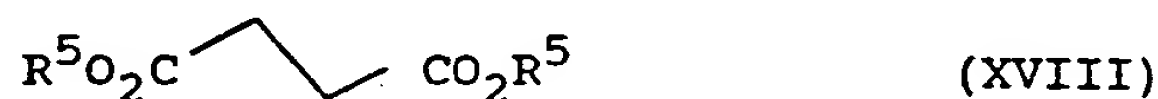
27
 28 The starting materials (compounds of general
 29 formulae IX, X, XIII and XIV) and reagents described
 30 above are either commercially available or may be
 31 produced by conventional processes from commercially

32
 33

1 available materials. For example, when R^1 represents a
 2 hydrogen atom, the substituted acid of general formula
 3 XIII may be prepared by reaction of an aldehyde XVII



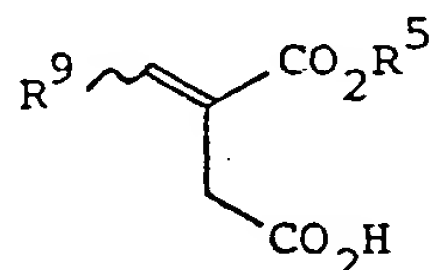
7 wherein R^9 represents a hydrogen atom or a C_1-C_5 alkyl
 8 C_1-C_5 alkenyl, phenyl (C_1-C_5) alkyl, cycloalkyl (C_1-C_5)
 9 alkyl or cycloalkenyl (C_1-C_5) alkyl group, with a
 10 succinate derivative of general formula XVIII,



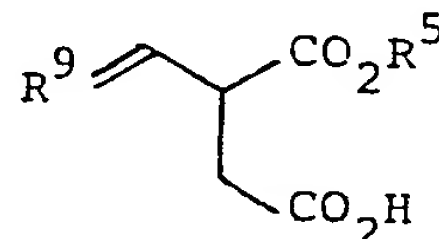
14 wherein:

16 R^5 represents a C_1-C_6 alkyl or benzyl group

18 under base catalysis to give a mixture of acids of
 19 general formulae XIXa and XIXb



(XIXa)

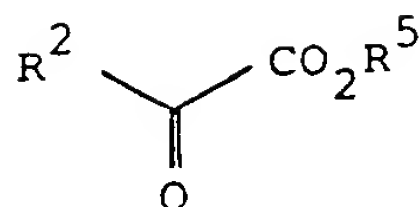


(XIXb)

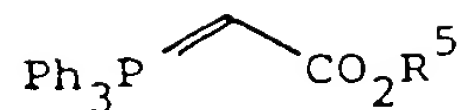
26 which by hydrogenation, esterification and hydrolysis
 27 can be converted to the acids of the general formula
 28 XIII.

30 Alternatively an ester of general formula XX may be
 31 reacted with an ester stabilised phosphorane of general
 32 formula XXI

33

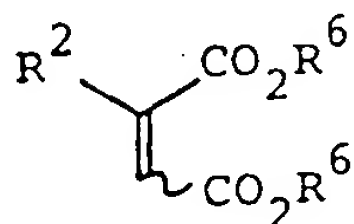


(XX)



(XXI)

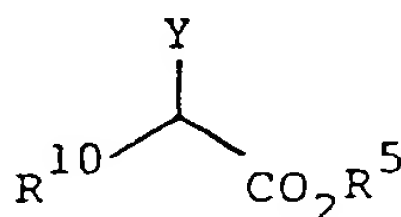
to yield a compound of general formula XXII



(XXII)

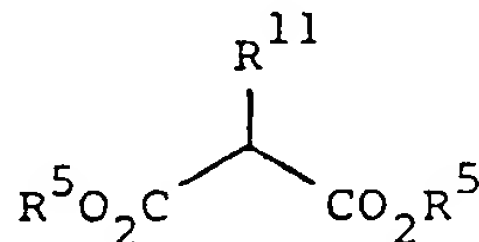
wherein R^5 represents a C_1 - C_6 alkyl group, which can be further converted by hydrogenation to the acids of general formula XIII.

In addition the substituted esters may be prepared by reacting an ester of the general formula XXIII



(XXIII)

wherein Y represents halo and R^5 is as defined above and R^{10} is either R^1 or R^2 as defined above, with a malonate derivative of the general formula XXIV



(XXIV)

1 wherein R^{11} is R^2 or R^1 as defined above, and the
2 alternative to that substituent employed in the halo
3 ester.

4
5 Compounds of general formulae III and IV are valuable
6 intermediates in the preparation of compounds of
7 general formula I. According to a third aspect of the
8 invention, there is therefore provided a compound of
9 general formula III. According to a fourth aspect of
10 the invention, there is provided a compound of general
11 formula IV.

12
13 As mentioned above, compounds of general formula I are
14 useful in human or veterinary medicine as they are
15 active inhibitors, of metalloproteases involved in
16 tissue degradation.

17
18 According to a fifth aspect of the invention, there is
19 provided a compound of general formula I for use in
20 human or veterinary medicine, particularly in the
21 management (by which is meant treatment of prophylaxis)
22 of disease involving tissue degradation, in particular
23 rheumatoid arthritis, and/or in the promotion of wound
24 healing.

25
26 According to a sixth aspect of the invention, there is
27 provided the use of a compound of general formula I in
28 the preparation of an agent for the management of
29 disease involving tissue degradation, particularly
30 rheumatoid arthritis, and/or in the promotion of wound
31 healing. Compounds of general formula I can therefore
32 be used in a method of treating disease involving
33 tissue degradation, particularly rheumatoid arthritis,

1 and/or in a method of promoting wound healing, the
2 method in either case comprising administering to a
3 human or animal patient an effective amount of a
4 compound of general formula I.

5
6 The potency of compounds of general formula I to act
7 as inhibitors of collagenase (a metalloprotease
8 involved in tissue degradation) was determined by the
9 procedure of Cawston and Barrett, (Anal. Biochem., 99,
10 340-345, 1979) and their potency to act as inhibitors
11 of stromelysin was determined using the procedure of
12 Cawston et al (Biochem. J., 195, 159-165 1981), both of
13 which techniques are to be described more fully in the
14 examples and, to the extent that the law allows, are
15 incorporated by reference herein.

16
17 According to a seventh aspect of the invention, there
18 is provided a pharmaceutical or veterinary formulation
19 comprising a compound of general formula I and a
20 pharmaceutically and/or veterinarily acceptable
21 carrier. One or more compounds of general formula I may
22 be present in association with one or more non-toxic
23 pharmaceutically and/or veterinarily acceptable
24 carriers and/or diluents and/or adjuvants and if
25 desired other active ingredients.

26
27 According to an eighth aspect of the invention, there
28 is provided a process for the preparation of a
29 pharmaceutical or veterinary formulation in accordance
30 with the seventh aspect, the process comprising
31 admixing a compound of general formula I and a
32 pharmaceutically and/or veterinarily acceptable
33 carrier.

1 Compounds of general formula I may be formulated for
2 administration by any route and would depend on the
3 disease being treated. The may be in the form of
4 tablets, capsules, powders, granules, lozenges, liquid
5 or gel preparations, such as oral, topical, or
6 sterile parenteral solutions or suspensions.

7
8 Tablets and capsules for oral administration may be in
9 unit dose presentation form, and may contain
10 conventional excipients such as binding agents, for
11 example syrup, acacia, gelatin, sorbitol, tragacanth,
12 or polyvinyl-pyrrollidone; fillers for example
13 lactose, sugar, maize-starch, calcium phosphate,
14 sorbitol or glycine; tableting lubricant, for example
15 magnesium stearate, talc, polyethylene glycol or
16 silica; disintegrants, for example potato starch, or
17 acceptable wetting agents such as sodium lauryl
18 sulphate. The tablets may be coated according to
19 methods well known in normal pharmaceutical practice.

20
21 Oral liquid preparations may be in the form of, for
22 example, aqueous or oily suspensions, solutions,
23 emulsions, syrups or elixirs, or may be presented as a
24 dry product for reconstitution with water or other
25 suitable vehicle before use. Such liquid
26 preparations may contain conventional additives such
27 as suspending agents, for example sorbitol, syrup;
28 methyl cellulose, glucose syrup, gelatin,
29 hydrogenated edible fats; emulsifying agents, for
30 example lecithin, sorbitan monooleate, or acacia;
31 non-aqueous vehicles (which may include edible
32 oils), for example almond oil, fractionated coconut
33 oil, oily esters such as glycerine, propylene glycol,

1 or ethyl alcohol; preservatives, for example methyl or
2 propyl p-hydroxybenzoate or sorbic acid, and if
3 desired conventional flavouring or colouring agents.

4
5 The dosage unit involved in oral administration may
6 contain from about 1 to 250 mg, preferably from about
7 25 to 250 mg, of a compound of general formula I. A
8 suitable daily dose for a mammal may vary widely
9 depending on the condition of the patient and will
10 ultimately depend on the judgement of the physician or
11 veterinarian. However, a dose of a compound of general
12 formula I of about 0.1 to 300mg/kg body weight,
13 particularly from about 1 to 100 mg/kg body weight may
14 be appropriate.

15
16 For topical application to the skin the drug may be
17 made up into a cream, lotion or ointment. Cream or
18 ointment formulations that may be used for the drug are
19 conventional formulations well known in the art, for
20 example, as described in standard text books of
21 pharmaceuticals such as the British Pharmacopoeia.

22
23 For topical applications to the eye, the drug may be
24 made up into a solution or suspension in a suitable
25 sterile aqueous or non-aqueous vehicle. Additives,
26 for instance buffers such as sodium metabisulphite or
27 disodium edeate; preservatives including bactericidal
28 and fungicidal agents, such as phenyl mercuric
29 acetate or nitrate, benzalkonium chloride or
30 chlorohexidine, and thickening agents such as
31 hypromellose may also be included.

32

33

1 The dosage employed for the topical administration
2 will, of course, depend on the size of the area being
3 treated. For the eyes each dose will be typically in
4 the range from 10 to 100 mg of the compound of general
5 formula I.

6
7 The active ingredient may also be administered
8 parenterally in a sterile medium. The drug
9 depending on the vehicle and concentration used, can
10 either be suspended or dissolved in the vehicle.
11 Advantageously, adjuvants such as a local anaesthetic,
12 preservative and buffering agents can be dissolved in
13 the vehicle.

14
15 For use in the treatment of rheumatoid arthritis the
16 compounds of this invention can be administered by
17 the oral route or by injection intra-articularly into
18 the affected joint. The daily dosage for a 70 kg
19 mammal will be in the range of 10 mgs to 1 gram of a
20 compound of general formula I.

21
22 The following examples illustrate the invention, but
23 are not intended to limit the scope in any way.

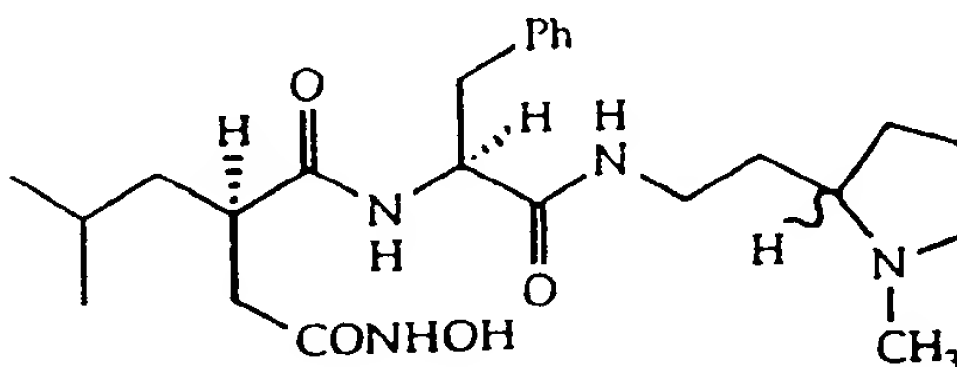
24
25 The following abbreviations have been used in the
26 Examples:-

27
28 DCC - Dicyclohexylcarbodiimide
29 DCM - Dichloromethane
30 DCU - Dicyclohexylurea
31 DIPE - Diisopropyl ether
32 DMF - N,N-dimethylformamide
33 HOBT - Hydroxybenztriazole

- 1 NMM - N-Methylmorpholine
2 TFA - Trifluoroacetic acid
3 THF - Tetrahydrofuran
4 WSCDI - N-(Dimethylaminoethyl)-N'-ethylcarbodiimide
5

6 Example 1

- 7
8 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalani-
9 ne-N-[(2-aminoethyl)-2(RS)-(1-methylpyrrolidine)]amide



- 10
11
12
13
14
15
16
17 (a) [4-Benzoyloxy-3-benzoyloxycarbonyl-2R-isobutyl-
18 succinyl]-L-phenylalanine methyl ester

- 19
20 Benzyl (2-benzoyloxycarbonyl-5-methyl-3R-tert-butoxy-
21 carbonyl)-hexanoate (52g, 115 mmol) was stirred at room
22 temperature with 5% water in TFA (250 ml) for 1.5h.
23 After this time the TFA was evaporated under reduced
24 pressure then the residue was azeotroped with toluene
25 (3 x 250 ml).

- 26
27 The crude acid from this reaction was dissolved in
28 DCM/DMF (4:1), then HOBT (16g, 118 mmol), NMM (12g, 118
29 mmol) and WSCDI (22g, 115 mmol) were added at room
30 temperature. After 20 minutes a further equivalent of
31 NMM (12g, 118 mmol) was added followed by
32 L-phenylalanine methyl ester hydrochloride (23g, 107
33 mmol). This solution was stirred overnight and then

1 concentrated under vacuum. The oily residue was
2 dissolved in DCM then washed with 10% citric acid
3 (2x250 ml), with 10% sodium bicarbonate (2x250 ml) and
4 once with saturated brine (250 ml). The organic
5 layer was dried (sodium sulphate), filtered then the
6 solvent removed under reduced pressure to give the
7 title compound as an oil (50.9g, 79%).

8
9 δ_{H} (250MHz, CDCl₃) 7.39-7.11 (15H,m), 5.19 (2H, d,
10 J=5Hz), 5.11 (2H, d, J=5Hz), 3.15-2.90 (2H, ABX), 0.79
11 (3H, d, J=6Hz), and 0.77 (3H, d, J=6Hz)

12
13 (b) Hydroxy-2R-isobutylsuccinyl]-L-phenylalanine methyl
14 ester

15
16 The product from above (50.9g, 91mmol) was dissolved in
17 ethanol (100ml) and stirred at room temperature with
18 activated charcoal pellets for 1h. 10% Palladium on
19 charcoal (20g) in ethyl acetate was slurried into the
20 ethanolic solution. Cyclohexene (20ml) in ethanol
21 (100ml) was added and the mixture was brought to reflux
22 for 5h. The reaction mixture was filtered to remove
23 the catalyst then the solvents evaporated under
24 reduced pressure to leave a yellow oil (29.8g). This
25 oil was taken up in xylene (500ml) and heated at
26 reflux for 10 minutes. The xylene was removed under
27 reduced pressure to leave the crude material as an oil
28 (26.5g).

29
30
31
32
33

1 (c) [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-
2 phenylalanine methyl ester

3
4 The crude acid (26.5g, 79mmol) was dissolved in
5 DCM/DMF (4:1, 500ml), then NMM (9.6g, 95mmol), HOBT
6 (12.8g 95mmol) and WSCDI (18.2g, 95mmol) added and the
7 mixture stirred at room temperature until tlc
8 indicated complete conversion to the activated ester
9 (about 10 minutes). To this solution containing the
10 active ester was added benzylhydroxylamine
11 hydrochloride (15.2g, 95mmol) and a further equivalent
12 of NMM (9.6g, 95mmol) in the solvent mixture (80ml).
13 After stirring at room temperature overnight DCM
14 (250ml) was added then the mixture washed with citric
15 acid (2x250ml), 10% sodium bicarbonate solution
16 (2x250ml) and brine (250ml) then finally dried over
17 sodium sulphate. The solution was filtered and the
18 solvent removed under reduced pressure to give an oil
19 (27.2g) which was purified by column chromatography
20 using ether as an eluant to give the title compound
21 (11g, 23.7mmol, 30%).

22
23 Δ_{H} (250MHz, CDCl₃) 7.47-7.09 (10H, m), 4.88 (2H,
24 s), 3.11 (2H, d, J=6Hz), and 0.87 (6H, m)

25
26 (d) [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-
27 phenylalanine

28
29 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
30 alanine methyl ester (9.5g, 21mmol) was dissolved in
31 methanol (200ml) and lithium hydroxide solution
32 (0.5N, 84ml, 42mmol) was added with stirring at room
33 temperature. When the reaction was complete, as judged

1 from tlc, the methanol was removed by evaporation and
2 the remaining aqueous phase was acidified to pH1 with
3 citric acid. The precipitated solid was filtered
4 off and dried, while the filtrate was extracted with
5 DCM (500ml) and dried over sodium sulphate. Solvent
6 removal from the organic phase left an oil (5.38g)
7 which could be recrystallised from diisopropyl ether
8 and methanol to give material which was identical with
9 the solid which precipitated during acidification.
10 These two batches were combined to give the title
11 compound (6.40g, 15mmol, 71%)

12
13 m.p. 161-162°C

14
15 ν_{\max} (KBr) 3300, 3020, 2980, 1710, 1650, 1630, 1550,
16 1265, 740, and 700 cm^{-1}

17
18 Δ_{H} (250MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$) 7.36 - 7.18 (10H, m),
19 4.77 (2H, s), 3.14 - 2.91 (2H, ABX), 2.06 - 2.00 (2H,
20 ABX), 1.50 (2H, bm), and 0.87 - 0.80 (6H, m)

21
22 Δ_{C} (62.9MHz, $\text{D}_6\text{-DMSO}$) 174.1, 173.1, 167.7, 137.9,
23 129.2-126.4, 76.9, 53.3, 40.7, 39.9, 36.8, 35.8, 25.3,
24 23.5, and 22.1

25
26 (e) [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
27 alanine-N-[(2-aminoethyl)-2(RS)-(1-methylpyrrolidine)]-
28 amide

29
30 [4-(N-Benzoyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
31 alanine (200mg, 0.47mmol) was dissolved in THF
32 (6ml) and cooled in ice. Triethylamine (52mg,
33 0.522mmol) was added together with

1 ethylchloroformate (50mg, 0.47mmol) and after 10
2 minutes 2-(2-aminoethyl)-N-methylpyrrolidine (67mg,
3 0.522mmol) in THF (1ml) was added. After 3h at room
4 temperature the reaction mixture was diluted with
5 ethyl acetate then washed with sodium bicarbonate
6 solution and brine, then dried over sodium sulphate.
7 Solvent removal under reduced pressure gave the
8 crude benzyl hydroxamate (220mg, 0.41mmol).

9
10 The crude material from above was dissolved in
11 cyclohexene/ethanol (10% solution, 5ml), 10% palladium
12 on charcoal (50mg) was added then the mixture refluxed
13 until starting material had disappeared by tlc (ca 30
14 minutes). The catalyst was removed by filtration, and
15 the solvent removed under reduced pressure to leave an
16 oil which could be crystallised by the addition of
17 hexane. The required product (150mg, 0.34mmol,
18 72%) was collected by filtration.

19
20 m.p. 156-158°C

21
22 Analysis calculated for $C_{24}H_{38}N_4O_4 \cdot 1/2H_2O$

23 Requires C 63.27 H 8.63 N 12.30

24 Found C 63.28 H 8.53 N 12.03

25

26 $\nu_{max}(\text{KBr})$ 3300, 2950, 1650, 1550, and 700cm^{-1}

27

28 Δ_{H} (250MHz, CDCl_3) 7.19 (5H, m), 4.41 (1H, bm),
29 2.99 (2H, m), 2.01 (4H, m), 1.61 (4H, m), 1.30 (4H, m),
30 and 0.72 (6H, m).

31

32

33

1 Example 2

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
4 alanine-N-[1-(2-aminoethyl)-piperidine]amide

5

6

7

8

9

10

11

12 Using the procedure described in Example 1e
13 [4-(N-benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
14 alanine (200mg, 0.47mmol) was coupled with
15 1-(2-aminoethyl)-piperidine (67mg, 0.522mmol) then the
16 product hydrogenated to give the title compound
17 (66mg, 0.15mmol, 31%)

18

19 m.p. 154-6°C (DCM/hexane)

20

21 $\nu_{\max}(\text{KBr})$ 3300, 2950, 1640, 700 cm^{-1}

22

23 Δ_{H} (250MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$) 7.2 (5H, s), 3.2 (1H,
24 bm), 2.4 (5H, bm), 1.6 (3H, bd), 0.85 (6H, m)

25

26 Example 3

27

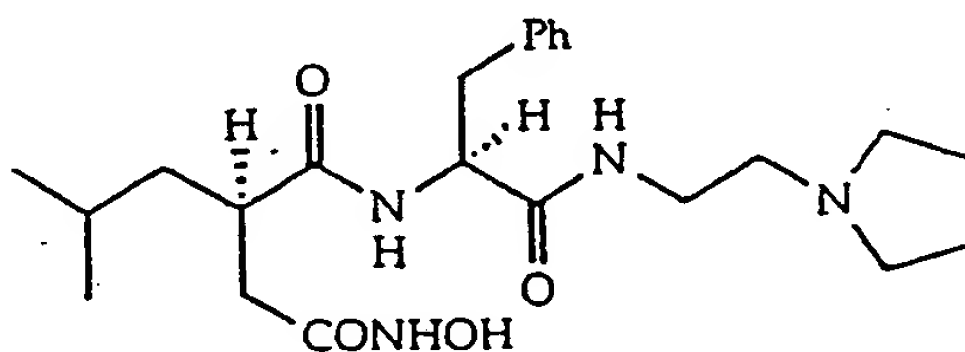
28 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
29 alanine-N-[1-(2-aminoethyl)-pyrrolidine]amide

30

31

32

33



1 Using the procedure described in Example 1e
2 [4-(N-benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
3 alanine (200mg, 0.47mmol) was coupled with
4 1-(2-aminoethyl)-pyrrolidine (117mg, 0.75mmol) then the
5 product hydrogenated to give the title compound.

6

7 m.p. 105-110°C

8 Analysis calculated for $C_{23}H_{36}N_4O_4 \cdot 0.4H_2O$

9 Requires C 62.82 H 8.43 N 12.74

10 Found C 63.09 H 8.18 N 12.23

11

12 Δ_H (250MHz, D_6 -DMSO) 8.14 (1H, d, J=8Hz, CONHCH),
13 7.78 (1H, t, J=5Hz, NHCH₂), 7.20 (5H, m, aromatic H),
14 4.42 (1H, m, PhCH₂CH), 3.10 - 2.62 (7H, m, NHCH₂CH₂,
15 PhCH₂, and CHCH₂CO), 2.44 - 2.32 (6H, m, CH₂CH₂CH₂CH₂
16 and NHCH₂CH₂N), 1.62 (4H, m, CH₂CH₂CH₂CH₂), 1.30 (2H,
17 m, CHCH₂CH), 0.98 (1H, m, (CH₃)₂CH), 0.74 and 0.78 (6H,
18 2xd, J=6Hz, (CH₃)₂CH).

19

20 Example 4

21

22 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
23 alanine-N-[1-(3-aminopropyl)-2(RS)-methylpiperidine]-
24 amide

25

26

27

28

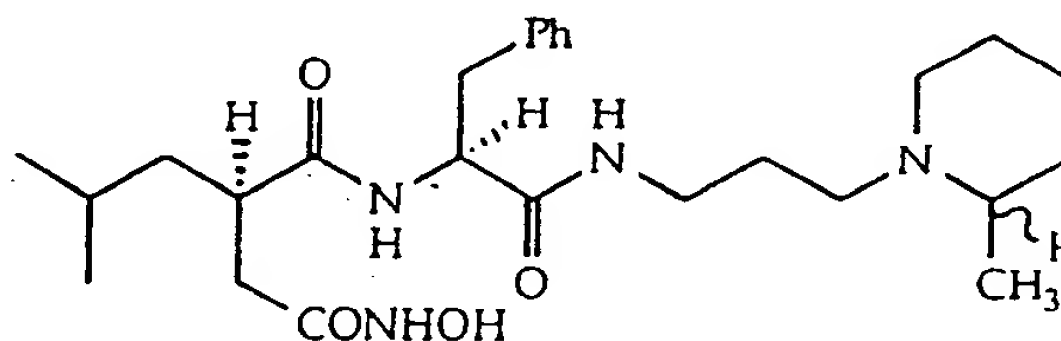
29

30

31

32

33



1 Using the procedure described in Example 1e
2 [4-(N-benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
3 alanine (200mg, 0.47mmol) was coupled with
4 1-(2-aminoethyl)-2-methylpiperidine (70mg, 0.75mmol)
5 then the product hydrogenated to give the title
6 compound.

7

8 m.p. 119-124°C

9

10 Delta_H (250MHz, D₆-DMSO) 8.10 (1H, d, J= 8Hz, CONHCH),
11 7.88 (5H, m, aromatic H), 4.38 (1H, m, PhCH₂CH), 3.10
12 - 2.58 (7H, m, NHCH₂, PhCH₂, and COCH₂CHCO), 2.42 -
13 2.22 (5H, m, NCHCH₂CH₂CH₂CH₂ and NHCH₂CH₂CH₂N), 2.12
14 - 1.34 (8H, m, NCHCH₂CH₂CH₂CH₂ and NHCH₂CH₂CH₂N),
15 1.24 - 1.16 (2H, m, CHCH₂CH), 1.00 (3H, d, J=4Hz,
16 CH₃CHN), and 0.96 - 0.62 (7H, m, (CH₃)₂CH).

17

18 Example 5

19

20 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
21 alanine-N-[2-(2-aminoethyl)-1-methylpyrrole]amide

22

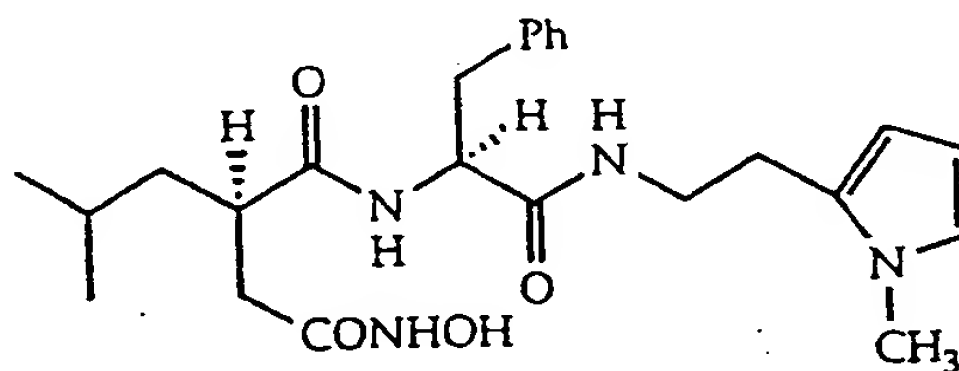
23

24

25

26

27



28 (a) Phenylalanine-N-[2-(2-aminoethyl)-1-methyl-
29 pyrrole]amide

30

31 To a solution of N-(benzyloxycarbonyl)-phenylalanine
32 (8.00g, 26.7mmol), 2-(2-aminoethyl)-1-methylpyrrole
33 (3.65g, 29.4mmol), HOBT (3.98g, 29.4mmol) and NMM

1 (2.97g, 29.4mmol) in DMF cooled to 0° was added a
2 solution of DCC (6.07g, 29.4mmol) in THF. After
3 addition was complete the reaction was left to stir
4 at room temperature overnight. The solvents were
5 removed under reduced pressure and the residual solid
6 was taken up in ethyl acetate and washed with water,
7 10% sodium bicarbonate and brine then dried over
8 sodium sulphate. Filtration and solvent removal gave
9 the crude benzyloxy protected material which was
10 converted to the free amine by dissolving in
11 ethanol/cyclohexene (10% solution, 150ml) adding 10%
12 palladium on charcoal and refluxing for 2h. This
13 mixture was filtered to remove the catalyst, the
14 ethanol was removed under reduced pressure, the
15 residue dissolved in ethyl acetate and extracted
16 with citric acid. Basification of the aqueous layer to
17 pH 12 with sodium hydroxide solution was followed by
18 extraction with ethyl acetate to give the title
19 compound (4.11g, 15 mmol, 57%)

20

21 Δ_{H} (250MHz, CDCl_3) 7.45 - 7.20 (7H, m, NH_2 +
22 aromatic H), 6.57 (1H, d, $J = 3\text{Hz}$), 6.06 (1H, d, $J =$
23 4Hz), 5.89 (1H, m), 3.50 (5H, m), 3.28 (1H, m), 2.71
24 (2H, m), and 1.26 (2H, t, $J = 7\text{Hz}$).

25

26 (b) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutyl-
27 succinyl]-L-phenylalanine-N-[2-(2-aminoethyl)-1-methyl-
28 pyrrole]amide

29

30 To a solution of phenylalanine-N-[2-(2-aminoethyl)-
31 1-methylpyrrole]amide (2.00g, 7.4mmol), 4-tert-butyl-
32 2R-isobutyl succinate (3.23g, 8.1mmol), HOBT (1.09g,
33 8.1mmol) and NMM (1.82g, 8.1mmol) in DMF cooled to 0°

1 was added DCC (1.67g, 8.1mmol) in THF. The
2 resultant mixture was allowed to warm to room
3 temperature then stirring continued for 72h. The
4 precipitated DCU was collected by filtration then
5 the solvents removed under reduced pressure. The
6 residual oil was dissolved in ethyl acetate, washed
7 with 10% sodium bicarbonate, water and brine then
8 dried over sodium sulphate. Solvent removal under
9 reduced pressure gave the crude product (5.48g) as an
10 oil. This material was purified by column
11 chromatography using 40% ethyl acetate in hexane as
12 eluant to give the desired isomer (1.45g, 2.2mmol, 30%)
13 completely separated from the
14 [4-benzyloxy-3-benzyloxycarbonyl-2S-isobutyl-
15 succinyl]-L-phenylalanine-N-[2-(2-aminoethyl)-1-methyl
16 pyrrole]amide isomer (1.04g, 1.6mmol, 22%).

17
18 Δ_H (250MHz, $CDCl_3$) 7.27 (10H, m, aromatic H), 7.19
19 (5H, m), 6.54 (1H, m), 6.02 (1H, t, $J=3\text{Hz}$), 5.17 -
20 5.01 (3H, m), 3.56 (3H, s), 3.31 (1H, m), 2.74 (2H,
21 m), 1.68 (1H, bm), 0.97 - 0.74 (3H, bm), 1.65 (3H, d,
22 $J=6\text{Hz}$), and 1.60 (3H, d, $J=6\text{Hz}$).

23
24 (c) [4-Hydroxy-2R-isobutylsuccinyl]-L-phenylalanine-N-
25 [2-(2-aminoethyl)-1-methylpyrrole]amide

26
27 [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-
28 L-phenylalanine-N-[2-(2-aminoethyl)-1-methylpyrrole]-
29 amide (1.45g, 2.3mmol) was dissolved in ethanol /
30 cyclohexene (10% solution), 10% palladium on charcoal
31 (0.14g) added and the mixture refluxed for 2h.
32 After this time tlc showed complete consumption of
33 starting material so the reaction was cooled,

1 filtered through celite and solvent removed under
2 vacuum. The resultant oil was taken up in toluene and
3 refluxed for two hours, solvent removal then gave the
4 crude material (1.09g, 2.6mmol) which was used without
5 further purification.

6
7 Δ_{H} (250MHz, CDCl_3) 7.21 (5H, m), 6.53 (1H, m), 5.99
8 (1H, s), 3.57 (1H, s), 3.50 (3H, m), 3.38 (1H, bm),
9 2.59 (2H, m), 2.37 (3H, s), 1.54 (1H, m), 1.30 (1H, m),
10 and 0.90 (6H, m).

11
12 (d) [4-(N-Benzoyloxyamino)-2R-isobutylsuccinyl]-L-
13 phenylalanine-N-[2-(2-aminoethyl)-1-methylpyrrole]amide

14
15 [4-Hydroxy-2R-isobutylsuccinyl]-L-phenylalanine-N-[2-
16 (2-aminoethyl)-1-methylpyrrole]amide (0.68g,
17 1.6mmol), benzylhydroxylamine (0.28g, 1.8mmol), NMM
18 (0.18g, 1.8mmol) and HOBT (0.24g, 1.8 mmol) were
19 dissolved in DMF and cooled to 0°. DCC (0.36g,
20 1.8mmol) in THF was added dropwise and when the
21 addition was complete the mixture was allowed to stir
22 overnight. The precipitated DCU was removed by
23 filtration, the solvents removed from the filtrate
24 under reduced pressure, the residue dissolved in ethyl
25 acetate (50ml) and washed with 10% sodium bicarbonate
26 (2x50ml), water (50ml) and brine (50ml) then dried
27 over sodium sulphate. Filtration and removal of the
28 ethyl acetate gave the crude product (1.25g) as an
29 oil. Further purification was achieved by column
30 chromatography using 2% methanol/DCM as eluant to give
31 the title compound (0.71g, 1.34mmol, 83%)

32

33

1 Δ_{H} (250MHz, CDCl_3) 7.47 - 7.16 (10H, bm), 6.52
2 (1H, t, $J = 2\text{Hz}$), 6.00 (1H, dd, $J = 3, 4\text{Hz}$), 5.75 (1H, m),
3 4.86 (2H, s), 3.44 (3H, s), 3.08 (2H, d, $J = 7\text{Hz}$), 2.50
4 (2H, m), 1.46 (1H, m), and 0.85 (6H, m)

5

6 (e) [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
7 alanine-N-[2-(2-aminoethyl)-1-methylpyrrole]amide

8

9 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
10 alanine-N-[2-(2-aminoethyl)-1-methylpyrrole]amide
11 (0.53g, 1.0mmol) was dissolved in cyclohexene/ethanol
12 (10% solution, 20ml), 10% palladium on charcoal
13 (50mg) was added then the mixture refluxed for 1h.
14 The catalyst was removed by filtration, and the solvent
15 removed under reduced pressure to leave an oil which
16 could be recrystallised from ethanol and diisopropyl
17 ether. The required product (196mg, 0.45mmol, 45%) was
18 collected by filtration.

19

20 m.p. 157-158°C

21

22 Δ_{H} (250MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$) 8.06 (2H, d, $J = 2\text{Hz}$),
23 7.97 (1H, m), 7.52 (5H, m, Ph), 6.87 (1H, d, $J = 1.8\text{Hz}$,
24 NH), 6.28 (1H, t, $J = 3\text{Hz}$, NH), 6.27 (1H, s, NH), 3.89
25 (3H, s, N-CH_3), 3.70 (2H, m), 3.46 (3H, m), 2.98 (2H,
26 m), 1.70 (2H, m), 1.43 (1H, m) and 1.20 (6H, m, $2 \times \text{CH}_3$).

27

28 Δ_{C} (62.9MHz, $\text{D}_6\text{-DMSO}$) 168.8, 165.6, 162.7, 132.5,
29 124.5, 123.7, 122.4, 120.6, 115.7, 100.9, 100.2, 72.1,
30 72.8, 73.5, 49.2, 36.3, 35.6, 35.0, 34.8, 34.0, 33.2,
31 32.8, 31.7, 30.4, 27.9, 23.9, 20.5, 19.7, 17.4, and
32 16.5

33

1 Example 6

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
4 alanine-N-(3-aminomethylpyridine)amide

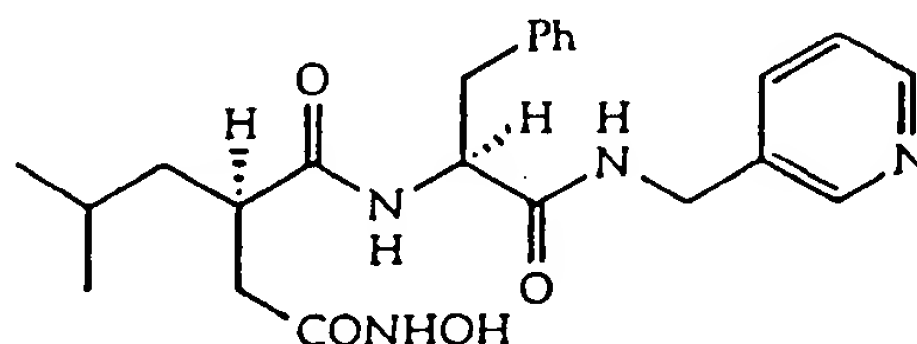
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6

7

8

9



10

11 The title compound was prepared by the method
12 described in Example 5 to give a compound with the
13 following characteristics

14

15 m.p. 184 - 185°

16

17 $[\alpha]_D = +2.1^\circ$ (c=1, MeOH)

18

19 $\nu_{\max}(\text{KBr})$ 3300, 1650, 1550, and 700 cm^{-1}

20

21 Analysis calculated for $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_4$

22 Requires C 64.77 H 7.09 N 13.14

23 Found C 64.51 H 7.08 N 13.21

24

25 Δ_{H} (250MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$) 8.68 (1H, bs), 8.41 (2H,
26 m), 7.95 (1H, d, J= 8Hz), 7.49 (1H, d, J= 8Hz), 7.15
27 (5H, m, aromatic H), 4.46 (2H, m), 4.27 (2H, d, J=
28 6Hz), 3.09 (1H, dd, J= 6, 14Hz), 2.88 (1H, dd, J= 10,
29 14Hz), 2.12 (1H, dd, J= 8, 16Hz), 1.95 (1H, dd, J=15,
30 6Hz), 1.30 (3H, m), and 0.70 (6H,m).

31

32

33

1 Example 7

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
4 alanine-N-(2-aminomethylpyridine)amide

5

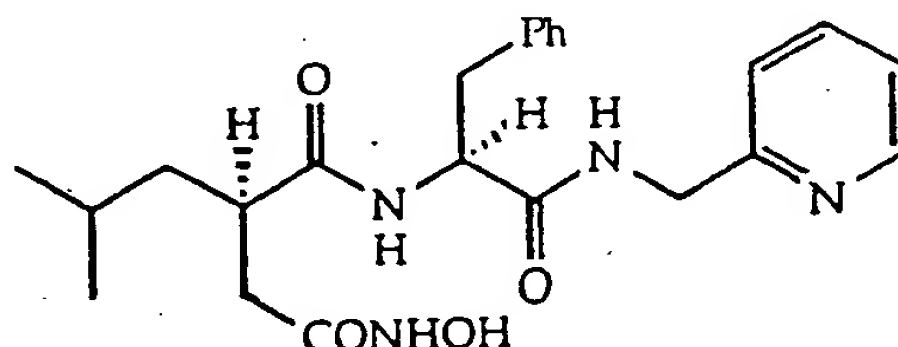
6

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8

9

10

11 The title compound was prepared by the method described
12 in Example 5 to give a compound with the following
13 characteristics

14

15 m.p. 165 - 167° (decomp.)

16

17 $[\alpha]_D = +1.8^\circ$ (c = 0.83, MeOH)

18

19 $\nu_{\max}(\text{KBr})$ 3280, 2960, 2920, 1715, 1680, and 750 cm^{-1}

20

21 Δ_H (250MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$, 1:3) 8.46 (2H, m), 8.05
22 (1H, partially obscured by solvent), 7.64 (1H, dt,
23 J=2,8 Hz), 7.22 (7H, m), 4.56 (1H, m), 4.42 (1H, s),
24 4.40 (1H, s), 3.17 (1H, dd, J=5,14 Hz), 2.96 (1H, dd,
25 J=9,14 Hz), 2.67 (1H, m), 2.16 (1H, dd, J=7,14 Hz),
26 2.00 (1H, dd, J=14,7 Hz), 1.37 (2H, m), 1.03 (1H, m),
27 0.79 (3H, d, J= 6Hz), and 0.75 (3H, d, J=6 Hz).

28

29 Δ_C (62.9MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$, 1:3) 174.2, 171.2,
30 167.9, 158.1, 148.4, 137.9, 136.3, 129.0, 127.9,
31 126.0, 121.7, 120.9, 78.7, 54.3, 44.3, 40.4, 37.0,
32 35.7, 25.2, 23.1, and 21.8.

33

1 Example 8

2

3 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
4 alanine-N-(4-aminomethylpyridine)amide

5

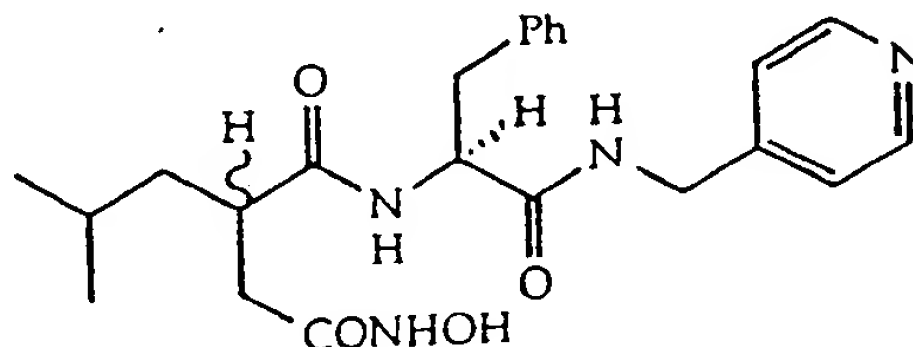
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9

10



11 The title compound was prepared by the method
12 described in Example 5 to give a 2:1 mixture of isomers
13 with the following characteristics

14

15 m.p. 189 - 192° (decomp)

16

17 $\nu_{\max}(\text{KBr})$ 3320, 3250, 2960, 2925, 1655, 1640, 1610,
18 1540, 730, and 700 cm^{-1}

19

20 Δ_{H} (250MHz, D_6 -DMSO) includes 10.4 (1H, bs), 7.24
21 (5H, m), 7.11 (2H, d, $J=6$ Hz), 4.51 (1H, m), 4.28 (1H,
22 s), 4.26 (1H, s), 0.76 (3H, d, $J=6$ Hz, major
23 diastereomer), 0.72 (3H, d, $J=6$ Hz, major
24 diastereomer), 0.69 (3H, d, $J=6$ Hz, minor
25 diastereomer), 0.58 (3H, d, $J=5$ Hz, minor diastereomer)

26

27 Δ_{C} (62.9MHz, D_6 -DMSO) Major isomer 174.2, 171.5,
28 167.7, 149.4, 148.4, 138.2, 129.3, 128.2, 126.4, 122.1,
29 54.3, 41.2, 40.5, 40.1, 37.2, 35.8, 25.3, 23.5, and
30 22.0 :Minor isomer 174.6, 171.7, 168.4, 149.5, 148.5,
31 138.6, 129.2, 128.1, 126.2, 122.2, 54.7, 41.5, 41.4,
32 40.9, 37.2, 36.8, 24.8, 23.6, and 21.9.

33

1 Example 9

2

3 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
4 alanine-N-(1-(3-aminopropyl)-imidazole)amide

5

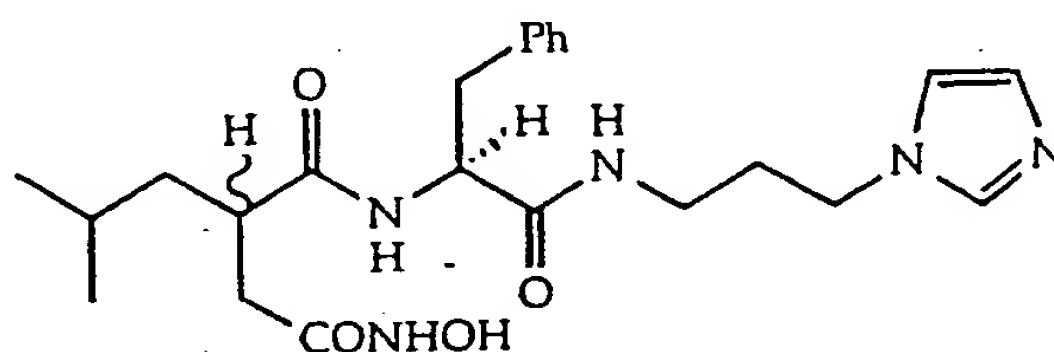
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7

8

9

10

11 The title compound was prepared by the method described
12 in Example 5 to give the title compound with the
13 following characteristics

14

15 m.p. 166-167

16

17 Δ_{H} (250MHz, CDCl_3) 7.35 (1H, m), 7.28 - 7.15 (5H,
18 m), 7.14 (1H, m), 7.00 (1H, s), 6.88 (1H, s), 4.97 (1H,
19 m), 4.00 - 3.90 (2H, m), 3.55 - 3.34 (2H, m), 3.32
20 (1H, m), 3.14 (1H, m), 2.59 (2H, m), 2.08 (2H, m),
21 1.94 (2H, m), 1.52 (1H, sep, $J=7\text{Hz}$), 1.29 (1H, m), and
22 0.91 - 0.73 (6H, m).

23

24 Δ_{C} (62.9MHz, CDCl_3) 179.8, 177.0, 168.7, 137.6,
25 137.0, 129.2, 128.6, 126.8, 118.6, 116.0, 77.6, 77.2,
26 76.6, 55.4, 44.5, 40.3, 38.1, 37.2, 34.6, 33.7, 30.6,
27 25.8, 22.8, and 21.7.

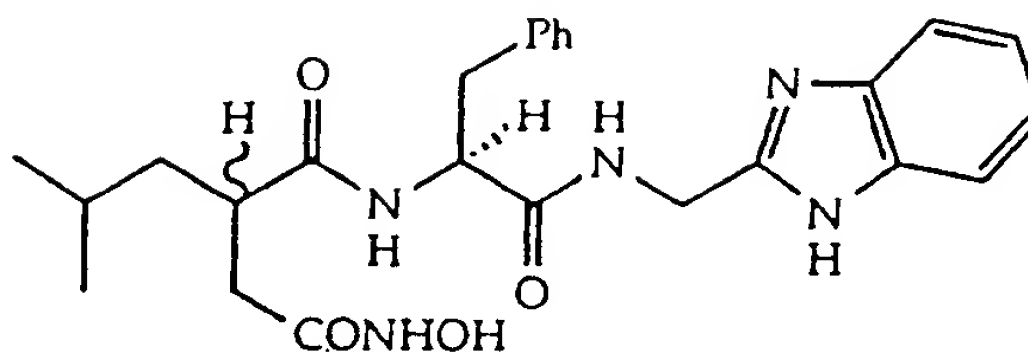
28

29 Example 10

30

31 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
32 alanine-N-(2-aminomethylbenzimidazole)amide

33



The title compound was prepared by the method described in Example 5 to give the title compound with the following characteristics

m.p. 217°

$[\alpha]_D = -77.4^{\circ}$ (c=1, MeOH)

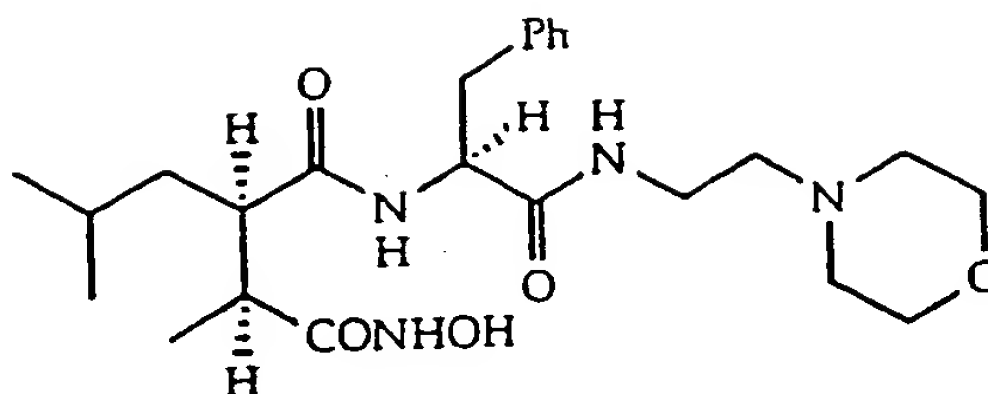
$\nu_{\max}(\text{KBr})$ 3280, 2960, 2920, 2860, 1650, 1550, 1510, 1440, 1275, 1030, 740, and 700 cm^{-1}

Δ_H (250MHz, CDCl_3/D_4 Methanol) 8.4 (1H, s, NH), 7.34 (2H, m), 7.26 (1H, s), 7.05 (5H, m), 4.48 (2H, m), 3.27 (1H, dd, $J=10,4\text{Hz}$), 3.17 (3H, m), 2.67 - 2.48 (2H, m), 2.20 - 1.92 (2H, m), 1.18 (1H, m), 0.73 (1H, m), and 0.52 (6H, m, $(\text{CH}_3)_2\text{CH}$)

Δ_C (62.9MHz, CDCl_3/D_4 Methanol) 171.1, 167.4, 164.7, 143.8, 132.0, 123.4, 123.1, 121.3, 117.3, 49.3, 36.3, 35.5, 31.6, 31.4, 30.2, 19.8, 17.8, and 16.0

Example 11

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholino]amide



(a) Phenylalanine-N-[4-(2-aminoethyl)morpholino]amide

To a solution of N-(Benzyloxycarbonyl)-phenylalanine (29.91g, 100mmol), 4-(2-aminoethyl)-morpholine (14.32g, 110mmol), HOBT (14.86g, 110mmol) and NMM (11.13g, 110mmol) in DCM / DMF (4:1) and DCC (6.07g, 29.4mmol) added. After addition was complete the reaction was left to stir at room temperature overnight. The solvents were removed under reduced pressure and the residual solid was taken up in ethyl acetate and washed with water, 10% sodium bicarbonate and brine. The ethyl acetate layer was then extracted with 3% hydrochloric acid the aqueous solution separated and basified to pH 11. This solution was extracted with ethyl acetate, dried over sodium sulphate then solvent removal gave the amine as a crude solid which was recrystallised from ethyl acetate/hexane (44.78g, 109mmol, 100%).

Δ_{H} (250MHz, CDCl_3) 7.56 (1H, m), 7.45 (5H, m), 7.39 (5H, bs), 7.15 (1H, d, $J=8\text{Hz}$), 5.17 (2H, s), 4.49 (1H, q, $J=7\text{Hz}$), 3.75 (3H, m), 3.40 (2H, t, $J=6\text{Hz}$), 3.24 (1H, dd, $J=5.5, 14\text{Hz}$), 3.05 (1H, m), and 2.51 (4H, bs).

1 Δ_C (62.9MHz, $CDCl_3$) 170.6, 136.8, 136.3, 129.4,
2 128.7, 128.6, 128.3, 128.1, 127.0, 77.7, 77.2, 76.6,
3 67.0, 66.7, 56.7, 56.4, 53.1, 39.3, and 35.5.

4
5 This material was converted to the free amine by
6 dissolving in ethanol/cyclohexene (10% solution),
7 adding 10% palladium on charcoal and refluxing for 2h.
8 The mixture was filtered to remove the catalyst, then
9 the ethanol was removed under reduced pressure to give
10 the title compound (19.16g, 69mmol, 69%).

11
12 (b) [4-tert-Butoxy-2R-isobutyl-3S-methylsuccinyl]-
13 L-phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide

14
15 To a solution of phenylalanine-N-[4-(2-aminoethyl)-
16 morpholine] amide (19.16g, 69mmol), 4-tert-butyl-2R-
17 isobutyl succinate (18.57g, 76mmol), HOBT (10.27g,
18 76mmol) and NMM (7.69g, 76mmol) in DMF cooled to 0°
19 was added DCC (15.68g, 76mmol) in THF. The resultant
20 mixture was allowed to warm to room temperature then
21 stirring continued over the weekend. The
22 precipitated DCU was collected by filtration then the
23 solvents removed under reduced pressure. The residual
24 oil was dissolved in ethyl acetate, washed with 10%
25 sodium bicarbonate, water and brine then dried over
26 sodium sulphate. Solvent removal under reduced
27 pressure gave the crude product (36.5g) as an oil.
28 This material was purified and the diastereomers
29 separated by careful column chromatography using 0 -
30 5% methanol in DCM as eluant to give the desired
31 isomer slightly contaminated with a lower running
32 isomer (7.86g, 15.6mmol, 23%)

33

1 Δ_{H} (250MHz, CDCl_3) 7.23 (5H, m), 6.54 (1H, d, J= 6.5Hz), 6.04 (1H, m), 3.60 (4H, m), 3.22 - 3.08 (2H, m), 2.95 (1H, m), 2.44 - 2.20 (8H, m), 1.71 (1H, m), 1.43 (9H, m), 1.12 (1H, m), 0.95 (2H, d, J=6Hz), and 0.83 (6H, t, J= 6Hz).

6

7 (c) [4-(N-Benzyloxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide

10

11 [4-tert-Butoxy-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide (2.37g, 4.7mmol) was dissolved in 5% water in TFA (15ml) with cooling and stirred for 90 minutes after which time tlc indicated that deprotection was complete. Removal of the excess TFA was achieved by azeotroping with xylene to give the crude acid which was used without further purification. This product was taken up in DCM / DMF (4:1, 20ml) and the pH adjusted to 7 by adding NMM. To this was added HOBt (0.76g, 5.6 mmol) and NMM (0.57g, 5.6mmol), then after cooling to 0°, WSCDI (1.08g, 5.6mmol). This mixture was left to stir at room temperature for 45 minutes, cooled in an ice bath and benzylhydroxylamine (0.90g, 5.6mmol) added and finally stirred overnight. The precipitated product was filtered off and dried to yield the title compound as a single isomer (1.62g, 2.9mmol, 52%).

28

29 Δ_{H} (250MHz, D_6 -DMSO) 8.26 - 8.23 (1H, d, J= 8Hz), 7.70 (1H, t, J=4Hz), 7.35 (5H, bs), 7.29 - 7.23 (5H, m), 4.74 (2H, s), 4.56 (1H, m), 3.55 (4H, t, J= 5Hz), 3.34 (5H, bs), 3.16 (2H, q, J= 6Hz), 2.90 (1H, m), 2.77

33

1 (1H, m), 2.33 (4H, t, J= 5Hz), 2.27 - 2.25 (2H, m),
2 1.94 (1H, m), 1.30 - 1.26 (2H, m), 0.80 (3H, d, J=6Hz),
3 0.72 (3H, d, J= 6Hz), and 0.42 (3H, d, J=7Hz).

4
5 (d) [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
6 L-phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide

7
8 [4-(N-Benzoyloxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
9 phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide
10 (8.1g, 14.6mmol) was dissolved in ethanol /
11 cyclohexene (10% solution, 100ml), 10% palladium on
12 charcoal (1.5g, 20% wt/wt) added and the mixture
13 refluxed for 30 minutes. Filtration to remove
14 catalyst followed by solvent removal under reduced
15 pressure gave a white solid which was recrystallised
16 from 5% methanol in ethyl acetate. Drying gave the
17 title compound (5.3g, 11.5mmol, 78%).

18
19 m.p. 205-210°C

20 Analysis calculated for C₂₄H₃₈N₄O₅

21 Requires C 62.32 H 8.28 N 12.11

22 Found C 62.05 H 8.22 N 11.97

23
24 Delta_H (250MHz, D₆-DMSO) 8.76 (1H, s, NH₂OH), 8.22
25 (1H, d, J= 8Hz, CONHCH), 7.72 (1H, bs, NHCH₂), 7.38 -
26 7.04 (5H, m, aromatic H), 4.56 (1H, m, PhCH₂CH), 3.64 -
27 3.42 (4H, m, CH₂OCH₂), 3.18 (2H, d, J= 5Hz, NHCH₂),
28 2.98 - 2.70 (2H, m, PhCH₂), 2.44 - 2.10 (8H, m,
29 NHCH₂CH₂ and CH₂NCH₂), 1.31 (2H, m, CH₂CH), 0.87 -
30 0.71 (7H, m, (CH₃)₂CH), and 0.41 (3H, d, J= 6Hz,
31 CH₃CH).

32

33

1 Delta_C (62.9MHz, D₆-DMSO) 173.5 (CONHOH), 171.2
 2 (CONHCONH), 138.2 - 126.2 (Aromatic C), 66.3
 3 (CH₂OCH₂), 57.3 (PhCH₂CH), 54.1 (NHCH₂CH₂), 53.4
 4 (CH₂NCH₂), 46.8 (NHCH₂), 37.4 (PhCH₂ and CHCHCO), 36.0
 5 (CH₂CH), 25.4 (Me₂CH), 24.2, 21.7 ((CH₃)₂CH), and
 6 16.1 (CH₃CH).

7

8 Example 12

9

10 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
 11 alanine-N-[4-(2-aminoethyl)-morpholine]amide

12

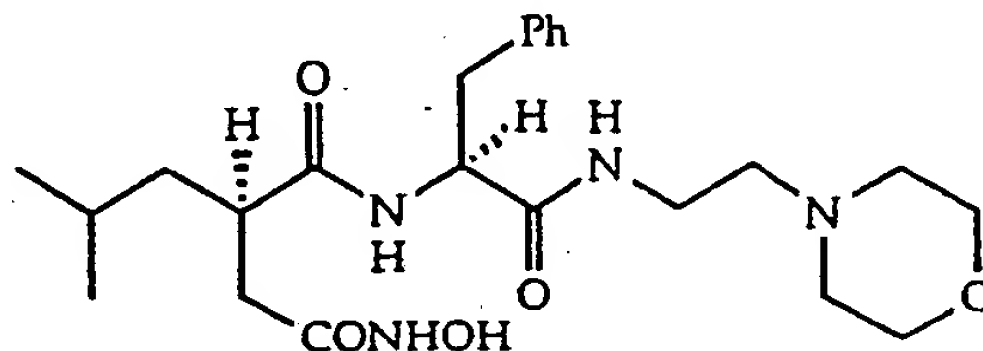
13

14

15

16

17



18 (a) [4-tert-Butoxy-2(RS)-isobutylsuccinyl]-L-phenyl-
 19 alaninebenzyl ester

20

21 To a solution of phenylalanine benzyl ester tosic acid
 22 salt (6.74g 17.6 mmol), 4-tert-butyl-2(RS)-isobutyl
 23 succinate (3.68g, 16.0 mmol), HOBT (2.38g, 17.6 mmol)
 24 and NMM (1.78g, 17.6 mmol) in DMF (20 ml) at 0° was
 25 added a solution of DCC (3.63g, 17.6 mmol) in THF
 26 (20ml). The resultant mixture was allowed to warm to
 27 room temperature then stirred overnight. The
 28 precipitated DCU was removed by filtration then the
 29 solution concentrated under reduced pressure. The
 30 residual oil was taken up in ethyl acetate and washed
 31 sequentitally with 10% sodium bicarbonate, dilute
 32 hydrochloric acid, water and finally brine. The
 33 solution was dried over sodium sulphate and the ethyl

1 acetate removed under reduced pressure. The crude
2 material thus produced was purified by column
3 chromatography using gradient elution of ethyl acetate
4 in DCM (0 - 15%) to give the title compound (3.16g,
5 6.7mmol, 42%)

6
7 (b) [4-tert-Butoxy-2(RS)-isobutylsuccinyl]-L-phenyl-
8 alanine

9
10 [4-tert-Butoxy-2(RS)-isobutylsuccinyl]-L-phenylalanine
11 benzyl ester (3.16g, 6.7mmol) was dissolved in
12 cyclohexene / ethanol (10% solution, 50ml), 10%
13 palladium on charcoal (2.0g) added and the mixture
14 refluxed for 10 minutes. The cooled solution was
15 filtered through celite and the solvent removed to
16 leave the title compound (2.25g, 6.0 mmol, 89%).

17
18 Δ_{H} (250MHz, CDCl₃) 7.27 - 7.16 (5H, m), 6.32 (1H,
19 m), 4.88 (1H, m), 3.18 (2H, m), 2.61 (2H, m), 2.33
20 (1H, m), 1.45 - 1.42 (9H, 2xs), 1.27 - 1.21 (2H, m),
21 and 0.88 - 0.82 (6H, m).

22
23 (c) [4-tert-Butoxy-2(RS)-isobutylsuccinyl]-L-phenyl-
24 alanine-N-[4-(2-aminoethyl)-morpholine]amide

25
26 [4-tert-Butoxy-2(RS)-isobutylsuccinyl]-L-phenylalanine
27 (2.27g, 6.01mmol), HOBT (0.89g, 6.62mmol), NMM
28 (0.67g, 6.62mmol) and 4-(2-aminoethyl)-morpholine
29 (0.86g, 6.62mmol) were dissolved in DCM / DMF (4:1,
30 50ml) and cooled to 0° while WSCDI (1.27g, 6.62mmol)
31 was added. After addition was complete the reaction
32 was allowed to warm to room temperature and then
33 stirred overnight. Solvents were removed under reduced

1 pressure then the residual oil taken up in ethyl
2 acetate and washed with water (200ml) and brine
3 (200ml). Drying the organic layer with sodium
4 sulphate, filtration and solvent removal gave desired
5 compound as a mixture of diastereomers (1.85g,
6 3.8mmol) which was deprotected without further
7 purification.

8
9 Δ_H (250MHz, $CDCl_3$) 7.18 (5H, m), 7.16 (1H, m), 6.48
10 (1H, m), 3.59 (4H, t, $J=4.5Hz$), 3.44 (1H, m), 3.24 -
11 3.02 (2H, m), 2.43 (1H, m), 2.36 (8H, m), 2.11 (1H,
12 m), 1.35 (9H, s), 1.09 (1H, d, $J=1Hz$), 1.06 (1H, d, $J=$
13 1Hz), and 0.72 - 0.69 (6H, m, $2 \times CH_3$)

14
15 (d) [4-(N-Benzyloxyamino)-2(RS)-isobutylsuccinyl]-L-
16 phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide

17
18 [4-tert-Butoxy-2(RS)-isobutylsuccinyl]-L-phenyl-
19 alanine-N-[4-(2-aminoethyl)-morpholine]amide (1.84g,
20 3.5mmol) was dissolved in water in TFA (5% solution,
21 20ml) and stirred for 2h at room temperature. The
22 excess TFA was removed by azeotroping with xylene to
23 give the crude acid. This material was mixed with HOBT
24 (0.57g, 4.15mmol), benzylhydroxylamine hydrochloride
25 (0.67g, 4.18mmol) and NMM (0.42g, 4.18mmol) and
26 dissolved in DCM / DMF (4:1, 35ml) and cooled to 0o
27 while WSCDI (0.80g, 4.18mmol) was added. The mixture
28 was warmed to room temperature and stirred overnight
29 then solvent removed under reduced pressure to leave an
30 oily residue.

31

32

33

1 Delta_H (250MHz, D₆-DMSO) 8.00 (1H, m), 7.53 (5H, m),
2 7.38 (5H, bs), 4.98 (1H, s), 3.79 - 3.75 (4H, t, J= 6
3 5Hz), 3.41 ((4H, s), 2.54 (8H, m), and 0.99 - 0.95 (6H,
4 2xd, J= 6Hz).

6 (e)
7 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
8 alanine-N-[4-(2-aminoethyl)-morpholine]amide

10 [4-(N-Benzyloxyamino)-2(RS)-isobutylsuccinyl]-l-phenyl-
11 alanine-N-[4-(2-aminoethyl)-morpholine]amide (250mg,
12 0.46 mmol), was dissolved in cyclohexene / ethanol
13 (10%, 5ml) and to it was added 10% palladium on
14 charcoal (250mg). The mixture was refluxed for 1 h at
15 room temperature, then the cooled solution filtered
16 through glass wool. The solvent was then removed
17 under reduced pressure to leave an oily solid which
18 was recrystallised from ethanol and DIPE (131mg, 0.30
19 mmol, 64%)

21 m.p. 151-153°C

Delta_H (250MHz, CDCl₃) 8.02 (2H, m), 7.55 (1H, m), 7.39 (5H, bs), 4.69 (1H, m), 3.31 - 3.28 (4H, m), 3.14 (1H, m), 2.63 - 2.54 (8H, m), 1.26 (1H, m), and 1.01 - 0.97 (6H, m).

28 Delta_C (62.9MHz, CDCl₃) 174.1, 171.0, 167.5, 138.3,
29 129.2, 128.1, 126.2, 66.3, 57.3, 54.1, 53.4, 37.4,
30 36.1, 25.3, 23.5, and 22.0

1 Example 13

2

3 [4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-phenyl-
4 alanine-N-[2-(2-aminoethyl)-pyridine]amide

5

6

7

8

9

10

11

12 The title compound was prepared by the method described
13 in Example 12 to give a compound with the following
14 characteristics

15

16 m.p. 174 -175°

17

18 $\nu_{\max}(\text{KBr})$ 3300, 2900, 1700, 1650, 1550, and 700 cm^{-1}

19

20 Analysis calculated for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_4 \cdot 0.2\text{H}_2\text{O}$

21 Requires C 64.90 H 7.35 N 12.61

22 Found C 64.90 H 7.35 N 12.76

23

24 Δ_{H} (250MHz, D_6 -DMSO) 8.88 (1H, bm), 8.49 (2H, d,
25 $J=4\text{Hz}$), 8.36 (1H, d, $J=9\text{Hz}$), 8.03 (2H, m), 7.70 (1H,
26 m), 7.21 (5H, m), 4.39 (1H, m), 3.46 (4H, m), 2.83
27 (4H, m), 2.17 (1H, dd, $J=9,15\text{ Hz}$), 1.92 (1H, dd, $J=$
28 12,3 Hz), and 0.76 (6H, m)

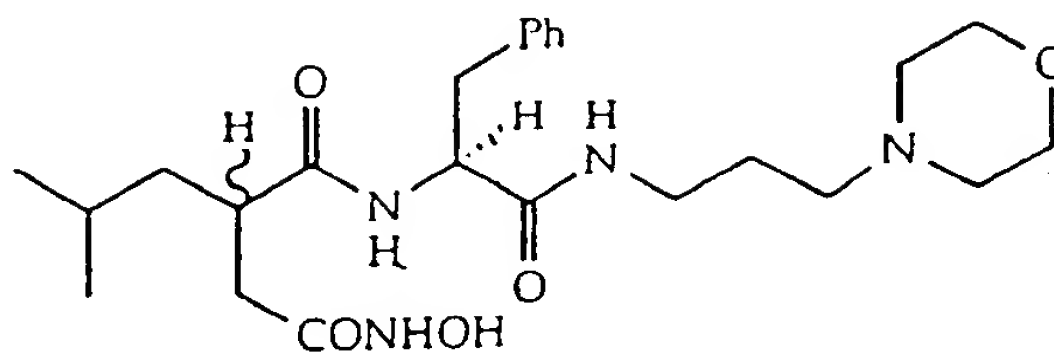
29

30 Example 14

31

32 [4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-phenyl-
33 alanine-N-[4-(2-aminopropyl)-morpholine]amide

57



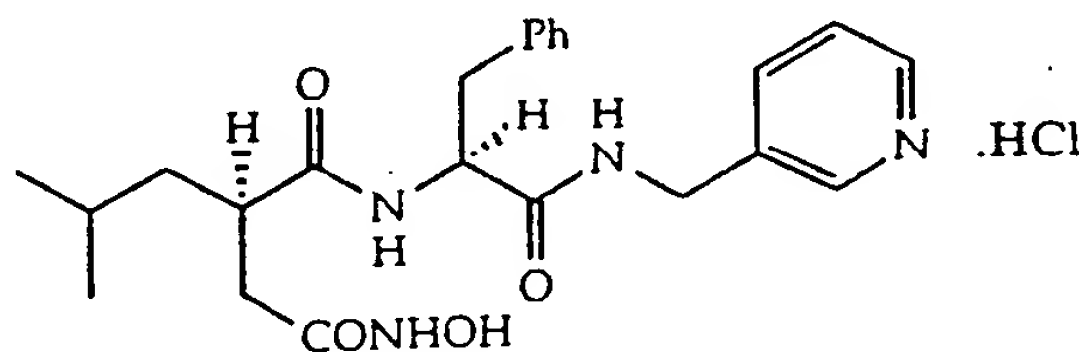
The title compound was prepared by the method described in Example 12 to give a compound with the following characteristics

m.p. 140-142°C

Δ_{H} (250MHz, CDCl_3 / D_6 -DMSO, 60 : 40) 8.15 (1H, d, $J=9\text{Hz}$), 8.03 (1H, s), 7.93 (1H, t, $J=4.5\text{Hz}$), 7.58 - 7.56 (5H, m), 6.92 (1H, t, $J=4\text{Hz}$), 4.02 (4H, m), 3.73 (1H, dd, $j=4,14\text{Hz}$), 3.50 - 3.44 (2H, m), 2.85 (1H, m), 2.78 - 2.66 (4H, m), 2.42 (2H, dd, $J=5,15\text{Hz}$), 1.64 (1H, m), 1.26 - 1.08 (2H, m), 1.04 (3H, d, $J=5\text{Hz}$), and 0.95 (3H, d, $J=6\text{Hz}$).

Example 15

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalanine-N-(3-aminomethylpyridine)amide hydrochloride.



SUBSTITUTE SHEET

1 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
2 alanine-N-(3-aminomethylpyridine)amide (100mg, 0.23
3 mmol) was dissolved in hydrochloric acid (2.34ml, 0.1M)
4 then the solution freeze dried to leave the title
5 compound as a white solid (64mg, 0.14mmol, 60%).

6
7 m.p: 87°

8
9 $[\alpha]_D = -32.2$ (c = 1, MeOH)

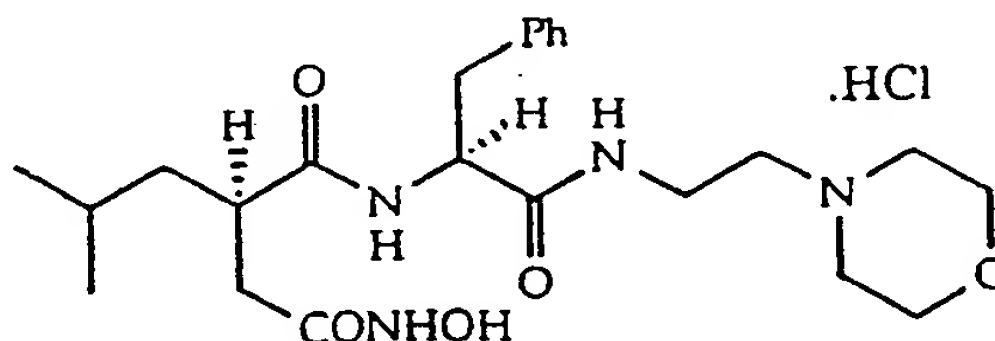
10
11 $\nu_{\max}(\text{KBr})$ 3300 - 3200, 3060, 2955, 2860, 1650, 1530,
12 1470, 1385, 700 and 680 cm^{-1}

13
14 Δ_H (250MHz, CDCl_3 / D_4 -Methanol) 9.30 (1H, s),
15 8.50 (1H, t, J=4Hz), 8.45 (1H, s), 8.42 (1H, d, J=
16 3Hz), 8.10 (1H, d, J= 6Hz), 7.65 (1H, t, J= 4Hz), 6.99
17 (5H, m), 4.20 (2H, m), 3.09 (2H, m), 3.02 (1H, d, J=
18 4Hz), 2.86 (1H, m), 2.38 (1H, m), 2.13 (1H, m), 1.93
19 (1H, dd, J= 3,10Hz), 1.08 - 1.02 (1H, m), 1.02 - 0.81
20 (2H, m) and 0.45 (6H, 2xd, J= 7Hz).

21
22 Δ_C (62.9MHz, CDCl_3 / D_4 -Methanol) 175.8, 172.0,
23 168.8, 144.3, 140.7, 139.8, 136.9, 128.6, 128.0, 126.3,
24 55.3, 41.4, 41.0, 39.6, 35.8, 35.1, 24.9, 22.2, and
25 21.1.

26
27 Example 16

28
29 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
30 alanine-N-[4-(2-aminoethyl)-morpholine]amide hydro-
31 chloride



1 The title compound was prepared by the method described
2 in Example 15 to give a compound with the following
3 characteristics

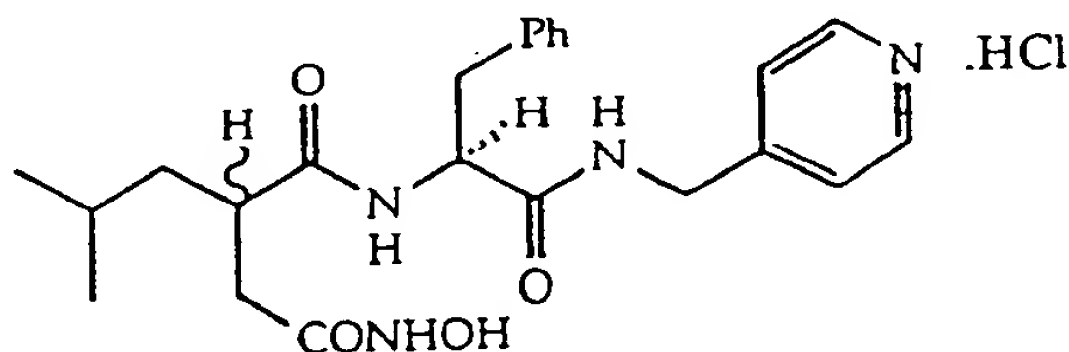
4
5 $[\alpha]_D = -37.5$ ($c = 1$, MeOH)

6
7 $\nu_{\max}(\text{KBr})$ 3450 - 3250, 2960, 2870, 1650, 1525, 1450,
8 and 1100 cm^{-1}

9
10 Δ_{H} (250MHz, CDCl_3 / D_4 -Methanol) 7.33 (5H, m,
11 Aromatic H), 4.75 (1H, s), 3.90 (2H, m), 3.45 (2H,
12 m), 3.20 - 3.00 (4H, m), 2.74 (1H, t, $J =$ Hz), 2.28
13 (2H, m), 1.50 - 1.10 (3H, m), and 0.82 (6H, m, 2xMe).

14
15 Example 17

16
17 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
18 alanine-N-(4-aminomethylpyridine)amide hydrochloride



26 The title compound was prepared by the method described
27 in Example 15 to give a compound with the following
28 characteristics

29 $[\alpha]_D = -22.7$ ($c = 1$, MeOH)

30
31 $\nu_{\max}(\text{KBr})$ 3300 - 3200, 3160, 2960, 1640, 1550 - 1500,
32 1410, 1380, 1365, 1250, and 600 cm^{-1}

33

1 Analysis calculated for $C_{23}H_{31}N_4O_4Cl$

2 Requires C 59.67 H 6.75 N 12.10

3 Found C 57.01 H 6.59 N 11.27

4

5 Δ_H (250MHz, D_4 -Methanol) 8.74 (2H, dd, $J=10,3$ Hz),

6 7.96 (1H, d, $J=7$ Hz), 7.90 (2H, d, $J=7$ Hz), 7.84 (2H,

7 d, $J=7$ Hz), 7.28 (5H, m), 4.76 (1H, s), 4.65 (2H, s),

8 4.50 (1H, dd, $J=9,6$ Hz), 3.28 (1H, m), 3.12 (1H, m) 2.70

9 (1H, m), 2.37 (1H, m), 2.15 (1H, m), 1.34 (2H, m), 0.97
10 (1H, m), and 0.82 (6H, m, 2xMe).

11

12 Δ_C (62.9MHz, D_4 -Methanol) 177.7, 174.4, 170.8,

13 162.3, 142.4, 130.2, 129.9, 129.5, 127.7, 126.5, 126.4,

14 56.8, 43.4, 42.7, 37.5, 36.6, 26.5, 23.4, and 22.2

15

16 Example 18

17

18 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
19 phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide
20 hydrochloride

21

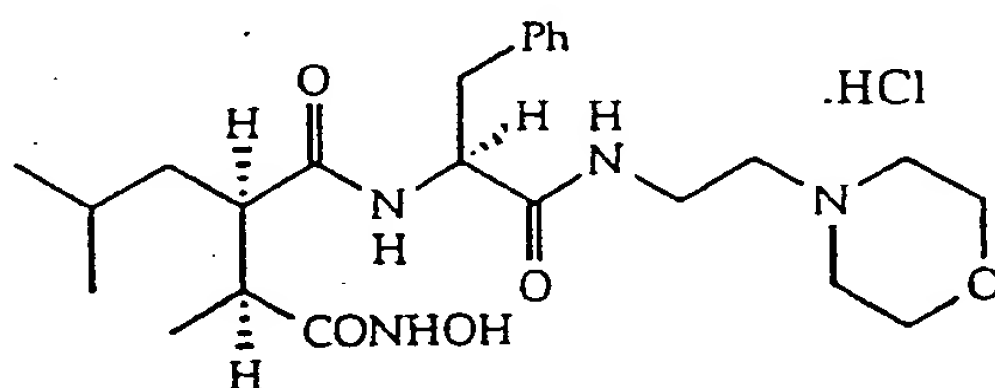
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23

24

25

26



27

28 The title compound was prepared by the method described
29 in Example 15 to give a compound with the following
30 characteristics

31

32 Analysis calculated for $C_{24}H_{39}N_4O_5Cl$

33 Requires C 55.75 H 7.99 N 10.84

Found C 55.65 H 7.81 N 10.81

1 Delta_H (250MHz, D₆-DMSO) 10.52 (1H, m, OH), 8.22 (2H,
2 m, CONH and CONH), 7.02 - 7.40 (5H, m, Aromatic H),
3 4.50 (1H, m, CHCH₂Ph), 4.04 - 3.82 (4H, m, CH₂OCH₂),
4 3.46 - 2.72 (12H, m, NHCH₂CH₂, CH₂NCH₂, PhCH₂, and
5 NHCH₂), 2.40 - 1.96 (2H, m, CHCHCO), 1.38 (2H, m,
6 CHCH₂CH), 1.00 - 0.84 (7H, m, CH(CH₃)₂), and 0.42 (3H,
7 d, J+ 4Hz, CH₃CH).

8

9 Example 19

10

11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
12 phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide
13 sodium salt.

14

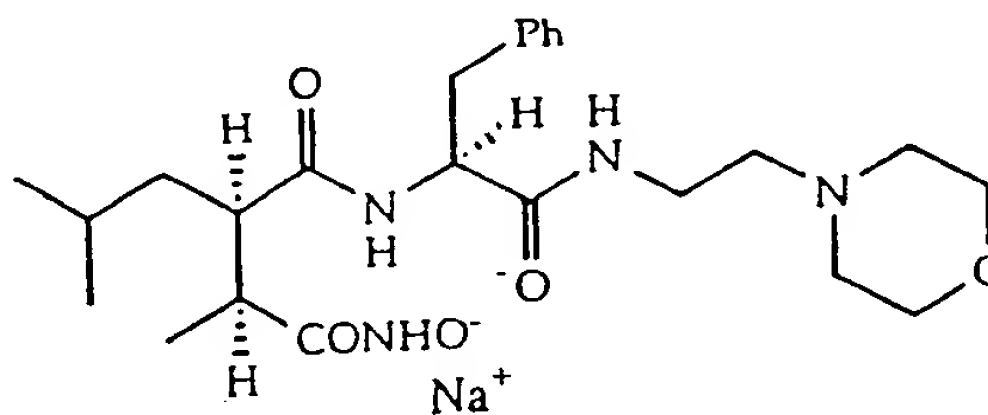
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16

17

18

19



20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
21 phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide
22 (92.4mg, 0.2mmol) was dissolved in methanol (20ml)
23 and sodium hydroxide solution (0.1M, 2.0ml) added to
24 give a homogeneous solution. The methanol was removed
25 under reduced pressure then the residual aqueous
26 solution freeze dried to give the title compound (97mg,
27 0.2mmol, 100%).

28

29 ν_{\max} (KBr) 3300, 2940, 1630, 1540, 1440, 1360, 1110,
30 860, and 700 cm⁻¹

31

32 Analysis calculated for C₂₄H₃₇N₄O₅Na.1.5H₂O

33 Requires C 56.37 H 7.88 N 10.95

1 Found C 56.44 H 7.40 N 10.61

2

3 Δ_{H} (250MHz, D_6 -DMSO) 8.26 (1H, d, $J=9\text{Hz}$, CONH),
4 7.74 (1H, m, CONH), 7.34 - 7.10 (5H, m, Aromatic H),
5 4.54 (1H, m, CHCH_2Ph), 3.58 (4H, m, CH_2OCH_2), 3.20
6 (2H, m, NHCH_2), 3.02 - 2.76 (2H, m, CH_2Ph), 2.38 - 2.20
7 (10H, m, NHCH_2CH_2 , CH_2NCH_2 , and CHCHCO), 1.38 (2H, m,
8 CHCH_2CH), 0.98 - 0.82 (7H, m, $\text{CH}(\text{CH}_3)_2$), and 0.40 (3h,
9 d, CH_3CH).

10

11 Example 20

12

13 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-1-phenyl-
14 alanine -N-[1-(3-aminopropyl)-imidazole]amide

15

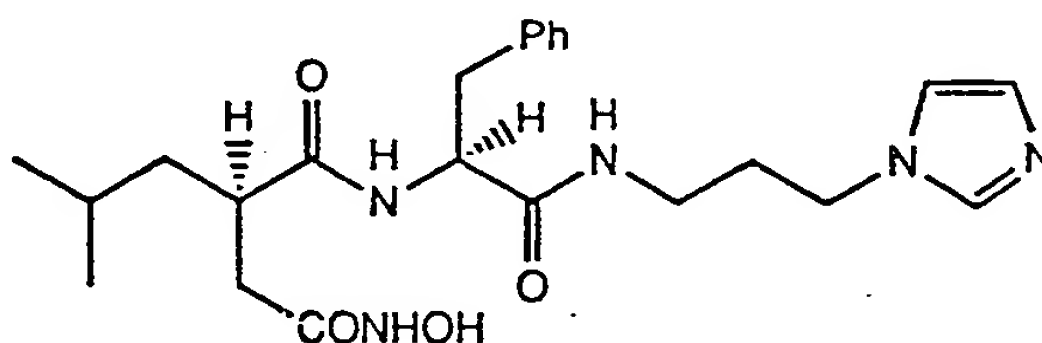
16

17

18

19

20



21

22

23 Prepared by the method described in Example 12 to give
24 a compound with the following characteristics.

25

26 m.p. 196-197°C

27

28 Analysis calculated for $\text{C}_{23}\text{H}_{30}\text{O}_4\text{N}_5$ (0.2 mols H_2O)

29

Requires C 61.80 H 7.39 N 15.68

30

Found C 61.86 H 7.47 N 15.81

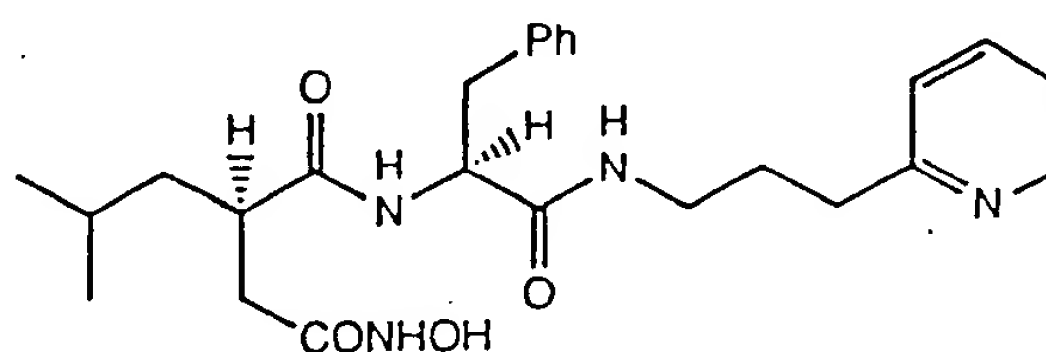
31

32 ν_{max} (KBr) 3280, 2960, 2860, 1640, 1540, 1520, 1440,
33 1375, 1240, 1110, 1080, 730, and 700.

Delta_H (62.9MHz, D₆-DMSO) 0.70, (3H, d, J=6Hz), 0.76, (3H, d, J=6Hz), 1.0 (1H, m) 1.29, (2H, m), 1.76, (2H, J=7Hz), 1.92 (1H, 2d, J=8, 8Hz), 2.05 (1H, 2d, J=7, 7Hz), 2.59 (1H, m), 2.85 (1H, dd, J=9, 14Hz), 3.0 (3H, m), 3.84 (2H, t, J=7Hz), 4.39 (1H, m), 6.97, (1H, s), 7.13, (1H, s), 7.23 (5H, m), 7.58 (1H, s), 8.08 (1H, m), 8.18 (1H, d, J=8Hz), and 8.54 (1H, s).

Example 21

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-1-phenyl-alanine -N-[2-(3-aminopropyl)-pyridine]amide



Prepared by the method described in Example 12 to give a compound with the following characteristics.

m.p. 169-170°C

Analysis calculated for C₂₅H₃₄N₄O₄ 1.3 mols H₂O

Requires C 62.76 H 7.11 N 11.72

Found C 63.15 H 7.32 N 11.36

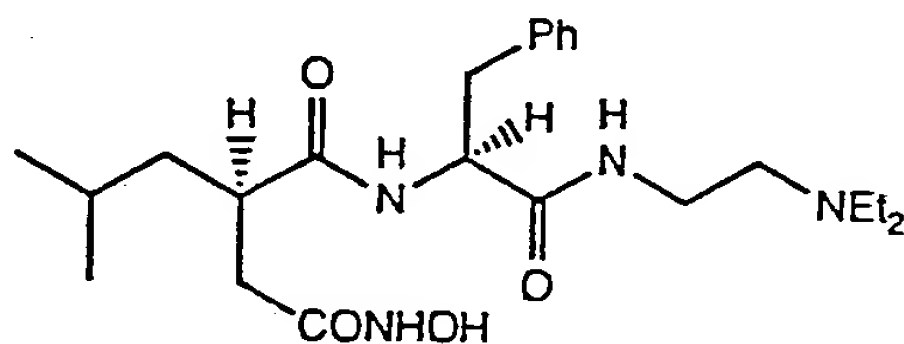
nu_{max} (KBr) 3280, 2950, 2920, 2860, 1660, 1535, 1435, 1000, 750, 700, and 635.

1 Δ_H (250MHz, D_6 -DMSO) 0.68, (3H, d, $J=6\text{Hz}$), 0.76
2 (3H, d, $J=6\text{Hz}$), 0.99 (1H, m), 1.34 (2H, m), 1.77, (2H,
3 t, $J=7\text{Hz}$), 2.03 (2H, m), 2.65 (3H, m), 2.86 (1H, m),
4 3.08 (3H, m), 4.44 (1H, m), 7.20 (7H, m), 7.49 (1H,
5 t, $J=7\text{Hz}$), 8.00 (1H, t, $J=5\text{Hz}$), 8.14 (1H, d, $J=8\text{Hz}$),
6 and 8.47 (1H, d, $J=4\text{Hz}$).
7

8 Δ_C (62.9MHz, D_6 -DMSO) 22.0, 23.4, 25.3, 29.0, 34.8,
9 35.8, 37.41, 38.4, 40.6, 40.8, 54.2, 121.3, 122.9,
10 126.3, 128.1, 129.2, 136.5, 149.1, 161.3, 167.7, 171.0,
11 174.0, and 175.3.
12
13

14 Example 22
15

16 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
17 alanine -N-[2-aminoethyl)-N,N-diethylamine]amide
18



26 Prepared by the method described in Example 12 to give
27 a compound with the following characteristics.

28
29 m.p. 62 -65°C
30

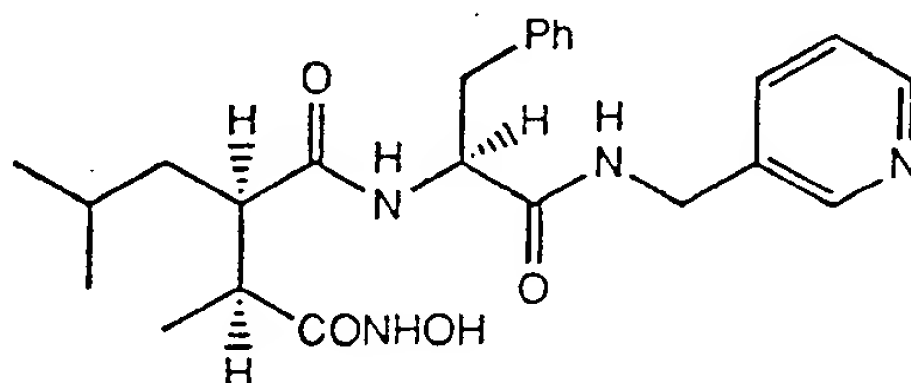
31 ν_{\max} (KBr) 3260, 3060, 2960, 2640, 1380, 1060, 745,
32 and 700.
33

1 Delta_H (250MHz, D₆-DMSO) 0.76, (3H, d, J=6Hz), 0.77
2 (3H, d, J=6Hz),
3 0.96 (3H, d, J=7Hz), 1.24 (2H, m), 1.92 (1H, m), 2.14
4 (2H, m), 2.50 (5H, bm), 2.80 (1H, dd, J=13,10Hz), 2.99
5 (1H, d, J=5Hz), 3.10 (4H, bm), 3.44 (5H, bm), 4.40 (2H,
6 m), 7.21 (5H, m), 7.78 - 7.91 (1H, m), and 8.12 - 8.37
7 (1H, d, J=8Hz).

8
9 Delta_C (62.9MHz, D₆-DMSO) 11.6, 11.6, 22.0, 23.5, 25.3,
10 35.3, 36.7, 46.7, 51.3, 54.1, 126.2, 128.1, 129.2,
11 138.3, 167.3, 170.9, and 178.2.

12
13 Example 23

14
15 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-l-
16 phenylalanine-N-[3-aminomethyl-pyridine]amide
17



26 Prepared by the method described in example 11 to give
27 a compound with the following characteristics.

28 m.p. 236-238°C

29 Analysis calculated for C₂₄H₃₂N₄O₄ (Contains 4% ash)

30 Requires C 62.81 H 7.03 N 12.15

31 Found C 62.74 H 7.03 N 12.36
32
33

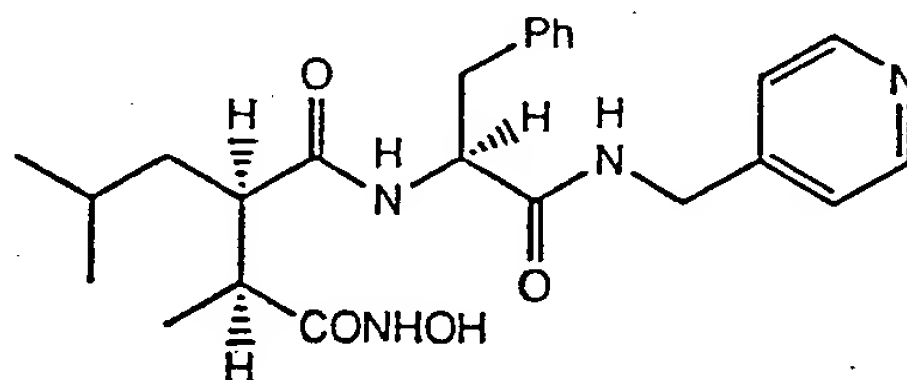
1 ν_{\max} (KBr) 3270, 3060, 2950, 2920, 1630, 1540, 1425,
2 1365, 1280, 1230, 1030, and 700.

3
4 Δ_H (250MHz D_6 -DMSO) 8.53 (1H, t, J=6Hz), 8.44 (2H,
5 dd, J=2, 5Hz),
6 8.34 (1H, d, J=8Hz), 7.54 (1H, dt, J=2, 8Hz), 7.31-7.14
7 (6H, m), 4.61 (1H, m), 4.28 (2H, t, J=5Hz), 2.97 (1H,
8 dd, J=5, 13Hz), 2.83 (1H, dd, J=13, 11Hz), 2.50 (1H,
9 m), 1.95 (1H, dd, J=6, 10Hz), 1.27 (3H, m), 0.84 (1H,
10 m), 0.74 (3H, d, J=6Hz), 0.67 (3H, d, J=6Hz),
11 and 0.42 (3H, d, J=7Hz).

12
13 Δ_C (62.9MHz, D_6 -DMSO) 172.4, 171.6, 171.5, 148.9,
14 148.1, 137.9, 135.01, 34.9, 129.3, 128.1, 126.3, 123.5,
15 54.2, 46.6, 36.4, 25.4, 21.6, and 16.1.

16
17 Example 24

18
19 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-1-
20 phenylalanine-N-[4-aminomethyl-pyridine]amide



29 Prepared by the method described in Example 11 to give
30 a compound with the following characteristics.

31
32 m.p. 227-230°C
33

1 Analysis calculated for $C_{24}H_{32}N_4O_4$ - (Contains 5% ash)

2 Requires C 62.16 H 6.95 N 12.08

3 Found C 62.13 H 7.06 N 11.96

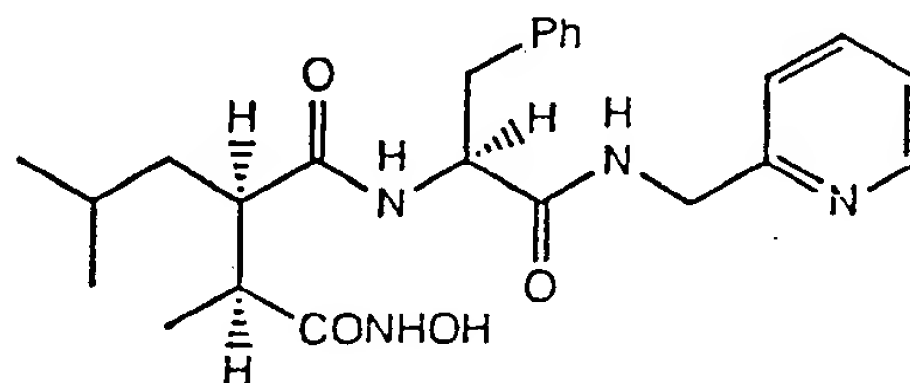
4
5 ν_{\max} (KBr) 3300, 2960, 2935, 1640, 1605, 1560, 1440,
6 1370, 1030, and 700.

7
8 Δ_H (250MHz, D_6 -DMSO) 0.47 (3H, d, $J=7$ Hz), 0.69 (3H,
9 d, $J=6$ Hz), 0.76 (3H, d, $J=6$ Hz), 0.83 (1H, m), 1.29 (2H,
10 m), 1.36 (1H, m), 1.98 (1H, dd, $J=7, 10$ Hz), 2.39 (1H,
11 td, $J=10, 3$ Hz), 2.84 (1H, dd, $J=10, 13$ Hz), 2.99 (1H,
12 dd, $J=5, 14$ Hz), 4.27 (2H, q, $J=3$ Hz), 4.65 (1H, m), 7.13
13 (2H, dd, $J=2, 4$ Hz), 7.28 (4H, m), 8.35 (1H, d, $J=8$ Hz),
14 8.44 (2H, dd, $J=2, 4$ Hz), 8.54 (1H, t, $J=6$ Hz), and 8.53
15 (H, s)

16
17 Δ_C (62.9MHz, D_6 -DMSO), 16.2, 21.6, 24.2, 25.4,
18 37.5, 41.2, 46.7, 54.7, 122.0, 126.4, 128.2, 129.4,
19 138.1, 148.4, 149.5, 171.4, 171.7, and 173.6.

20
21 Example 25

22
23 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-1-
24 phenylalanine-N-[2-aminomethyl-pyridine]amide



1 Prepared by the method described in Example 11 to give
2 a compound with the following characteristics.

3
4 m.p. 244-245°C

5
6 Analysis calculated for $C_{24}H_{32}N_4O_4$

7 Requires C 65.43 H 7.32 N 12.72

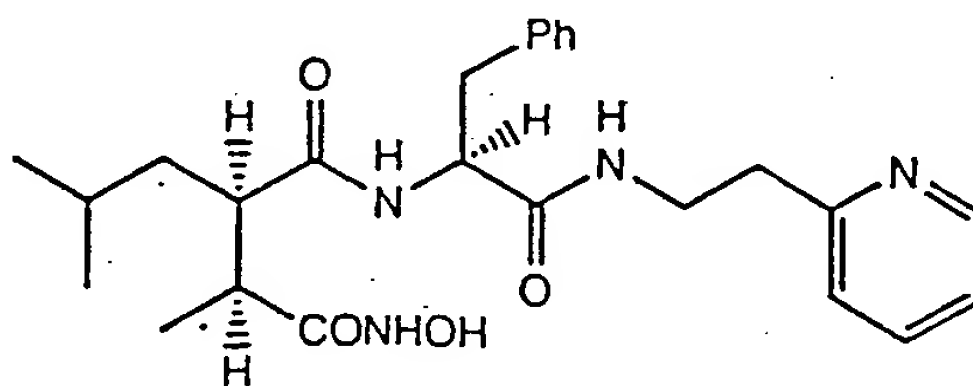
8 Found C 65.18 H 7.13 N 12.60

9
10 ν_{\max} (KBR) 3260, 3060, 2950, 1630, 1430, 1280, 1230,
11 1005, 950, 745, 700, and 630.

12
13 Δ_{H} (250MHz, D_6 -DMSO) 0.42 (3H, d, J=7Hz), 0.68 (3H,
14 d, J=6Hz), 0.76 (3H, d, J=6Hz), 0.84 m (1H, m), 1.30
15 (2H, m), 1.98 (1H, m), 2.49 (1H, m), 2.83 (1H, dd,
16 J=11, 13Hz) 3.03 (1H, dd, J=13, 5Hz), 4.35 (2H, d,
17 J=6Hz) 4.66 (1H, m), 7.22 (8H, m), 7.67 (1H, dd, J=2,
18 8Hz), 8.32 (1H, d, J=8Hz), and 8.47 (2H, m).

19
20 Example 26

21
22 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-1-
23 phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide
24



1 Prepared by the method described in Example 11 to give
2 a compound with the following characteristics.

3
4 m.p. 224-226°C

5
6 Analysis calculated for $C_{25}H_{34}O_4N_4 \cdot 0.4 H_2O$

7 Requires C 65.04 H 7.37 N 12.15

8 Found C 65.01 H 7.40 N 12.04

9
10 ν_{max} (KBr) 3295, 3060, 2960, 2915, 2865, 1655, 1630,
11 1530, 1435, 1370, 1385, 1240, 1210, 1035, 1005, 720,
12 690, and 635.

13
14 Δ_H (250MHz, D_6 -DMSO) 0.43 (3H, d, J=7Hz), 0.73 (3H,
15 d, J=6Hz), 0.82 (3H, d, J=6Hz), 1.28 (2H, m), 1.94 (1H,
16 m), 2.36 (1H, m), 2.73 (1H, m), 2.84 (3H, m), 3.37 (4H,
17 m), 4.58 (1H, m), 7.19 (6H, m), 7.68 (1H, dt, J=2, 8Hz)
18 7.96 (1H, t, J=5Hz), 8.24 (1H, d, J=8Hz), and 8.52
19 (1H, d, J=6Hz).

20
21 Δ_C (62.9MHz, D_6 -DMSO) 16.1, 21.7, 24.2, 25.4, 37.4,
22 37.5, 38.5, 46.8, 54.2, 121.6, 123.2, 126.2, 128.1,
23 129.3, 136.6, 138.3, 149.2, 150.1, 171.3, 171.4, and
24 173.4.

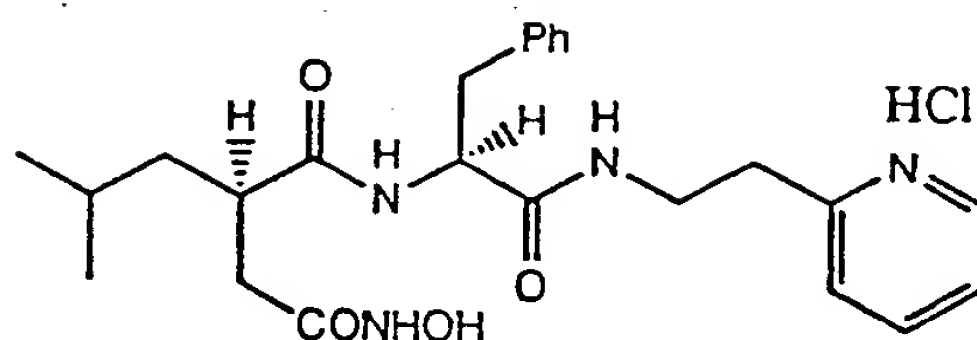
25
26 Example 27

27
28 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
29 alanine-N-[2-(2-aminoethyl)-pyridine]amide hydro-
30 chloride.

31

32

33



Prepared by the method described in Example 15 to give a compound with the following characteristics.

m.p. 88°C-92°C

Analysis calculated for $C_{24}H_{33}N_4O_4$ Cl. 3% Ash

Requires C 58.61 H 6.76 N 11.39

Found C 58.41 H 6.90 N 11.42

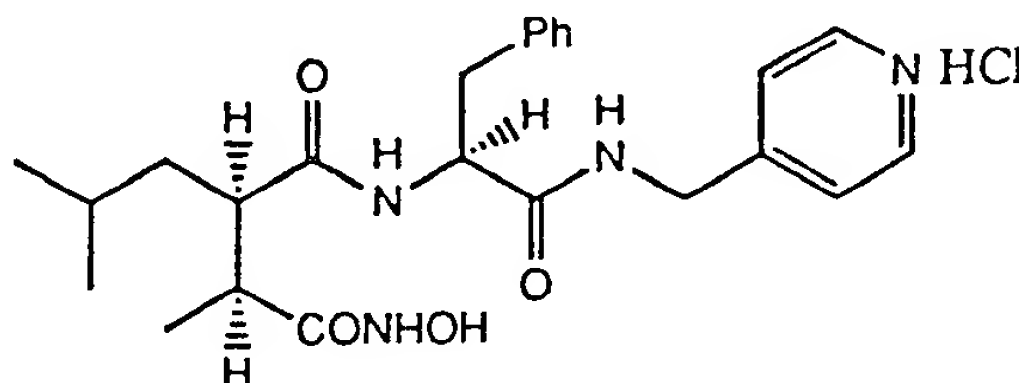
ν_{\max} (KBr) 3120, 3040, 2445, 1635, 1535, 1435, 695, and 625.

Δ_H (250MHz, D_6 -DMSO) 1.02, (3H, d) 1.14 (2H, m), 1.23 (1H, m), 1.67 (2H, m), 2.42 (1H, 2d, $J=15$, 3Hz), 2.73 (1H, m), 2.90 (2H, m), 3.12m (1H), 3.63 (4H, m), 3.98 (2H, m), 4.10 (1H, m), 4.83 (1H, t, $J=8$ Hz), 7.55 (1H, m, $J=5$ Hz), 8.02 (t, 2H, $J=7$ Hz), 8.08 (1H, s), 8.11 (1H, s), 8.38 (1H, d, $J=7$ Hz), 8.34 (2H, m), and 9.00 (1H, d, $J=6$ Hz).

Δ_C (62.9MHz, D_6 -DMSO) 26.60, 26.71, 27.80, 28.18, 29.63, 29.93, 38.71, 39.35, 40.38, 40.80, 41.41, 43.44, 46.25, 46.90, 59.59, 59.77, 82.36, 82.88, 83.40, 128.40, 128.67, 130.91, 131.34, 131.87, 132.85, 133.73, 133.83, 142.97, 147.47, 148.52, 160.66, 161.08, 173.58, 174.07, 176.48, 176.79, and 180.01.

1 Example 28

2
3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-1-phenyl-
4 alanine-N-[4-aminomethyl-pyridine]amide hydrochloride.
5



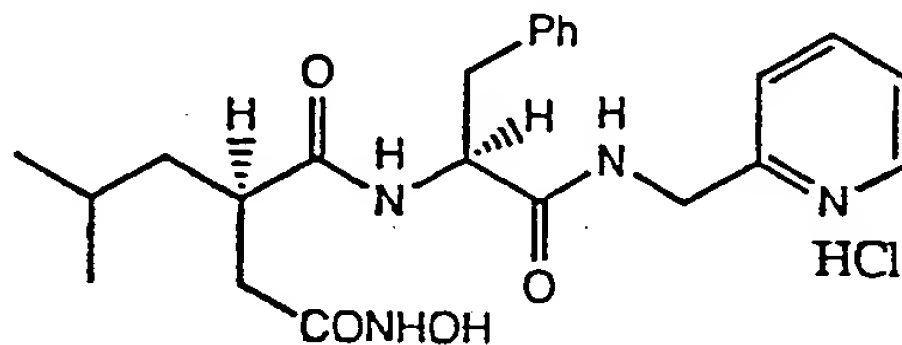
16 Prepared by the method described in Example 15 to give
17 a compound with the following characteristics.

18 Δ_H (250MHz, D_6 -DMSO) 0.47 (3H, d, $J=7$ Hz), 0.69 (3H,
19 d, $J=6$ Hz), 0.76 (3H, d, $J=6$ Hz), 0.83 (1H, m), 1.29 (2H,
20 m), 1.36 (1H, m), 1.98 (1H, dd, $J=7, 10$ Hz), 2.39 (1H,
21 td, $J=10, 3$ Hz), 2.84 (1H, dd, $J=10, 13$ Hz), 2.99 (1H,
22 dd, $J=5, 14$ Hz), 4.27 (2H, q, $J=3$ Hz), 4.65 (1H, m), 7.13
23 (2H, dd, $J=2, 4$ Hz), 7.28 (4H, m), 8.35 (1H, d, $J=8$ Hz),
24 8.44 (2H, dd, $J=2, 4$ Hz), 8.54 (1H, t, $J=6$ Hz), and 8.53
25 (H, s)

26
27 Δ_C (62.9MHz, D_6 -DMSO), 16.2, 21.7, 24.2, 25.4,
28 37.5, 41.2, 46.7, 54.7, 122.0, 126.4, 128.2, 129.4,
29 138.1, 148.4, 149.5, 171.4, 171.7, and 173.6
30
31
32
33

1 Example 29

2
3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-1-phenyl-
4 alanine-N-[2-aminomethyl-pyridine]amide hydrochloride.
5



14 Prepared by the method described in Example 15 to give
15 a compound with the following characteristics.

16 Analysis for $C_{23}H_{31}N_4O_4Cl$

17 Requires C 59.67 H 6.73 N 12.10

18 Found C 53.98 H 6.39 N 11.12
19

20 Δ_H (250MHz, $CDCl_3/D_6$ -DMSO, 1:3) 8.46 (2H, m), 8.05
21 (1H, partially obscured by solvent), 7.64 (1H, dt,
22 $J=2,8$ Hz), 7.22 (7H, m), 4.56 (1H, m), 4.42 (1H, s),
23 4.40 (1H, s), 3.17 (1H, dd, $J=5,14$ Hz), 2.96 (1H, dd,
24 $J=9,14$ Hz), 2.67 (1H, m), 2.16 (1H, dd, $J=7,14$ Hz),
25 2.00 (1H, dd, $J=14,7$ Hz), 1.37 (2H, m), 1.03 (1H, m),
26 0.79 (3H, d, $J=6$ Hz), and 0.75 (3H, d, $J=6$ Hz).
27

28 Δ_C (62.9MHz, $CDCl_3/D_6$ -DMSO, 1:3) 174.2, 171.2,
29 167.9, 158.1, 148.4, 137.9, 136.3, 129.0, 127.9, 126.0,
30 121.7, 120.9, 78.7, 54.3, 44.3, 40.4, 37.0, 35.7, 25.2,
31 23.1, and 21.8.
32
33

1 Example 30

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
4 alanine-N-[2-(3-aminopropyl)-pyridine]amide
5 hydrochloride.

6

7

8

9

10

11

12

13

14 Prepared by the method described in Example 15 to give
15 a compound with the following characteristics.

16

17 Δ_{H} (250MHz, D_6 -DMSO) 0.68, (3H, d, $J=6\text{Hz}$), 0.76
18 (3H, d, $J=6\text{Hz}$), 0.99 (1H, m), 1.34 (2H, m), 1.77, (2H,
19 t, $J=7\text{Hz}$), 2.03 (2H, m), 2.65 (3H, m), 2.86 (1H, m),
20 3.08 (3H, m), 4.44 (1H, m), 7.20 (7H, m), 7.86 (2H, m),
21 8.13 (2H, m), 8.42 (1H, t, $J=7\text{Hz}$), and 8.75 (1H, d,
22 $J=5\text{Hz}$).

23

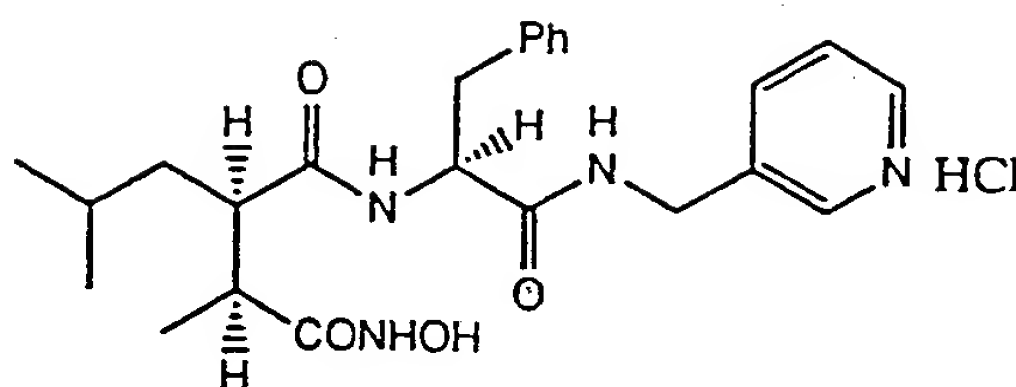
24 Δ_{C} (62.9MHz, D_6 -DMSO) 22.0, 23.4, 25.3, 29.0, 34.8,
25 35.8, 37.41, 38.4, 40.6, 40.8, 54.2, 121.3, 122.9,
26 126.3, 128.1, 129.2, 136.5, 149.1, 161.3, 167.7, 171.0,
27 174.0, and 175.3.

28

29 Example 31

30

31 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-l-
32 phenylalanine-N-[3-aminomethyl-pyridine]amide
33 hydrochloride.



Prepared by the method described in Example 15 to give a compound with the following characteristics.

ν_{\max} (KBr) 3270, 3060, 2950, 2920, 1630, 1540, 1425, 1365, 1280, 1230, 1030, and 700.

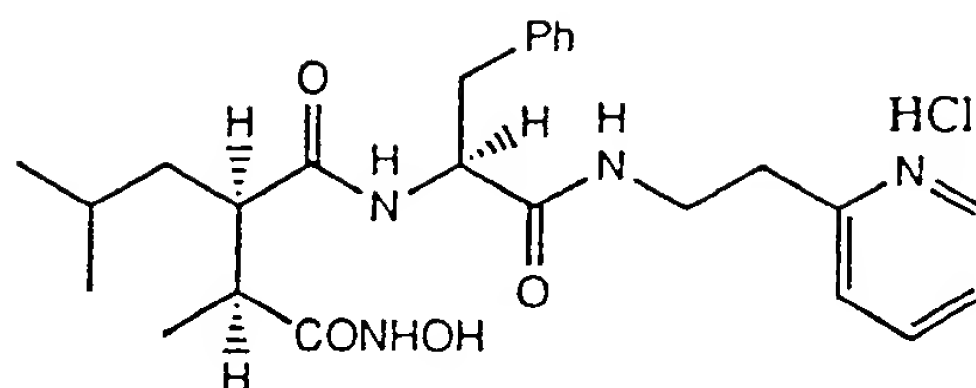
Δ_{H} (250MHz D_6 -DMSO), 8.87 (1H, t, $j=6\text{Hz}$), 8.76 (2H, d, $J=8\text{Hz}$), 8.39 (1H, d, $J=8\text{Hz}$), 8.23 (1H, d, $J=8\text{Hz}$), 7.91 (1H, dd, $J=8, 6\text{Hz}$), 7.31-7.14 (6H, m), 4.61 (1H, m), 4.28 (2H, t, $J=5\text{Hz}$), 2.97 (1H, dd, $J=5, 13\text{Hz}$), 2.83 (1H, dd, $J=13, 11\text{Hz}$), 2.50 (1H, m), 1.95 (1H, dd, $J=6, 10\text{Hz}$), 1.27 (3H, m), 0.84 (1H, m), 0.74 (3H, d, $J=6\text{Hz}$), 0.67 (3H, d, $J=6\text{Hz}$), and 0.42 (3H, d, $J=7\text{Hz}$).

Δ_{C} (62.9MHz, D_6 -DMSO) 172.4, 171.6, 171.5, 148.9, 148.1, 137.9, 135.0, 34.9, 129.3, 128.1, 126.3, 123.5, 54.2, 46.6, 36.4, 25.4, 21.6, and 16.1.

Example 32

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide hydrochloride.

75



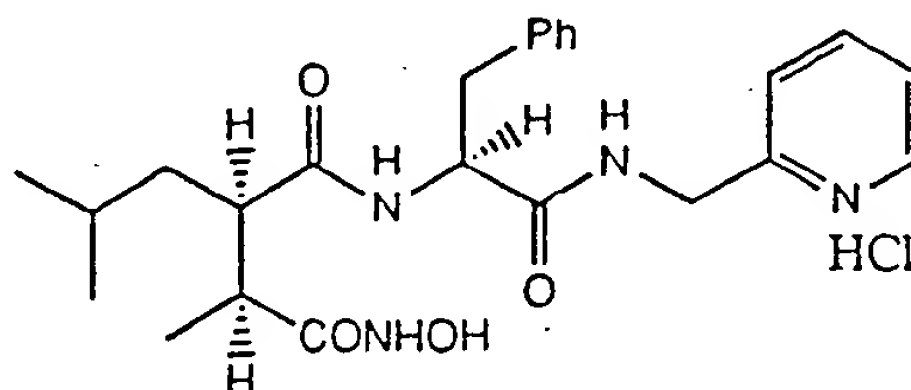
Prepared by the method described in Example 15 to give a compound with the following characteristics.

Δ_H (250MHz, D_6 -DMSO) 0.43 (3H, d, $J=7$ Hz), 0.73 (3H, d, $J=6$ Hz), 0.82 (3H, d, $J=6$ Hz), 1.28 (2H, m), 1.94 (1H, m), 2.36 (1H, m), 2.67 (1H, m), 2.86 (1H, dd, $J=14, 4$ Hz), 3.12 (2H, t, $J=6$ Hz), 3.58 (3H, m), 4.58 (1H, m), 7.19 (6H, m), 7.83 (2H, m), 8.20 (2H, m), 8.38 (1H, t, $J=7$ Hz), and 8.78 (1H, d, $J=5$ Hz).

Δ_C (62.9MHz, D_6 -DMSO) 16.1, 21.7, 24.2, 25.4, 37.4, 37.5, 38.5, 46.8, 54.2, 121.6, 123.2, 126.2, 128.1, 129.3, 136.6, 138.3, 149.2, 150.1, 171.3, 171.4, and 173.4.

Example 33

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine-N-[2-aminomethyl-pyridine]amide hydrochloride.



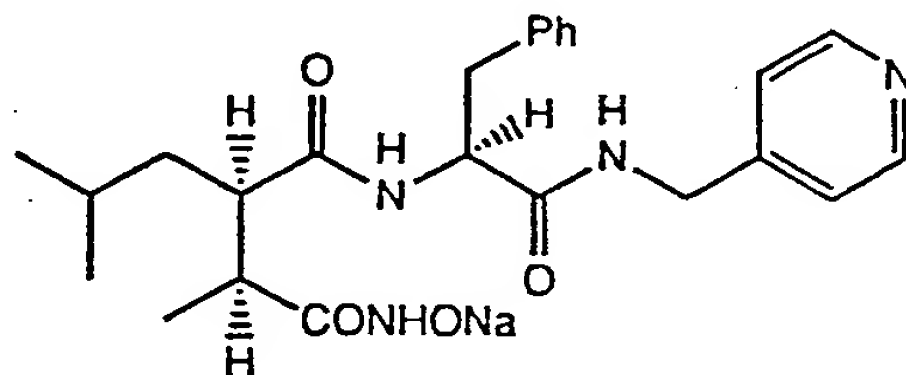
SUBSTITUTE SHEET

1 Prepared by the method described in Example 15 to give
2 a compound with the following characteristics.

3
4 Δ_{H} (250MHz, D_6 -DMSO) 0.42 (3H, d, $J=7\text{Hz}$), 0.68 (3H,
5 d, $J=6\text{Hz}$), 0.76 (3H, d, $J=6\text{Hz}$), 0.84 m (1H, m), 1.30
6 (2H, m), 1.98 (1H, m), 2.49 (1H, m), 2.83 (1H, dd,
7 $J=11, 13\text{Hz}$) 3.03 (1H, dd, $J=13, 5\text{Hz}$), 4.35 (2H, d,
8 $J=6\text{Hz}$) 4.66 (1H, m), 7.22 (8H, m), 7.48 (1h, t, $J=6\text{Hz}$),
9 7.96 (1H, dt, $J=2, 8\text{Hz}$), 8.33 (1H, d, $J=8\text{Hz}$), and 8.61
10 (2H, t, $J=6\text{Hz}$).
11
12

13 Example 34
14

15 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-l-
16 phenylalanine-N-[4-aminomethyl-pyridine]amide sodium
17 salt.
18



26 Prepared by the method described in Example 19 to give
27 a compound with the following characteristics.

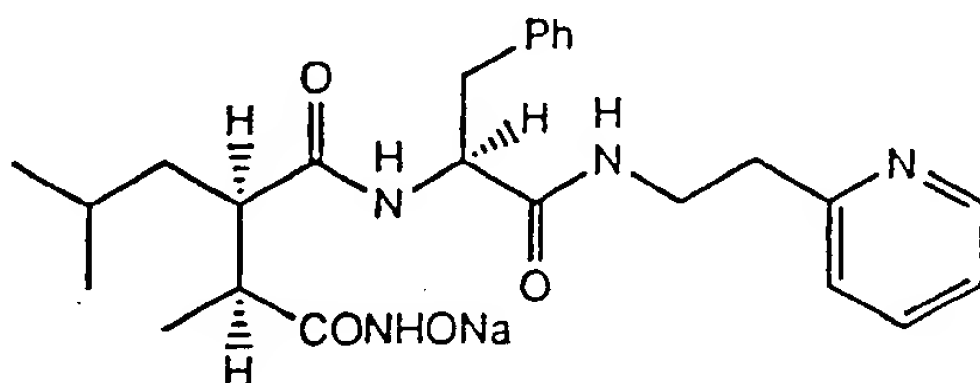
28
29 Δ_{H} (250MHz, D_6 -DMSO) 0.47 (3H, d, $J=7\text{Hz}$), 0.69 (3H,
30 d, $J=6\text{Hz}$), 0.76 (3H, d, $J=6\text{Hz}$), 0.83 (1H, m), 1.29 (2H,
31 m), 1.36 (1H, m), 1.98 (1H, dd, $J=7, 10\text{Hz}$), 2.39 (1H,
32 td, $J=10, 3\text{Hz}$), 2.84 (1H, dd, $J=10, 13\text{Hz}$), 2.99 (1H,
33 dd, $J=5, 14\text{Hz}$), 4.27 (2H, q, $J=3\text{Hz}$), 4.65 (1H, m), 7.13

1 (2H, dd, J=2, 4Hz), 7.28 (4H, m), 8.35 (1H, d, J=8Hz),
2 8.44 (2H, dd, J=2, 4Hz), 8.54 (1H, t, J=6Hz), and 8.53
3 (H, s)

4
5 Delta_C (62.9MHz, D₆-DMSO), 16.2, 21.6, 24.2, 25.4,
6 37.5, 41.2, 46.7, 54.7, 122.0, 126.4, 128.2, 129.4,
7 138.1, 148.4, 149.5, 171.4, 171.7, and 173.6.

8
9 Example 35

10
11 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-1-
12 phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide sodium
13 salt.



22 Prepared by the method described in Example 19 to give
23 a compound with the following characteristics.

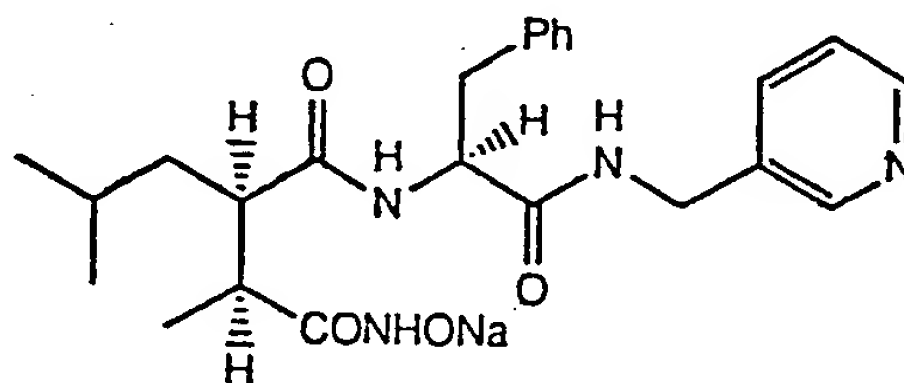
24
25 Delta_H (250MHz, D₆-DMSO) 0.43 (3H, d, J=7Hz), 0.73 (3H,
26 d, J=6Hz), 0.82 (3H, d, J=6Hz), 1.28 (2H, m), 1.94 (1H,
27 m), 2.36 (1H, m), 2.73 (1H, m), 2.84 (3H, m), 3.37 (4H,
28 m), 4.58 (1H, m), 7.19 (6H, m), 7.68 (1H, dt, J=2, 8Hz)
29 7.96 (1H, t, J=5Hz), 8.36 (1H, d, J=8Hz), and 8.52
30 (1H, d, J=6Hz).

31
32 Delta_C (62.9MHz, D₆-DMSO) 16.1, 21.7, 24.2, 25.4, 37.4,
33 37.5, 38.5, 46.8, 54.2, 121.6, 123.2, 126.2, 128.1,

1 129.3, 136.6, 138.3, 149.2, 150.1, 171.3, 171.4, and
2 173.4.

3
4 Example 36

5
6 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-1-
7 phenylalanine-N-[3-aminomethyl-pyridine]amide sodium
8 salt.



20 Prepared by the method described in Example 19 to give
21 a compound with the following characteristics.

22
23 ν_{\max} (KBr) 3270, 3060, 2950, 2920, 1630, 1540, 1425,
24 1365, 1280, 1230, 1030, and 700.

25 Δ_{H} (250MHz D_6 -DMSO) 8.53 (1H, t, J=6Hz), 8.44 (2H,
26 dd, J=2, 5Hz), 8.34 (1H, d, J=8Hz), 7.54 (1H, dt, J=2,
27 8Hz), 7.31-7.14 (6H, m), 4.61 (1H, m), 4.28 (2H, t,
28 J=5Hz), 2.97 (1H, dd, J=5, 13Hz), 2.83 (1H, dd, J=13,
29 11Hz), 2.50 (1H, m), 1.95 (1H, dd, J=6, 10Hz), 1.27
30 (3H, m), 0.84 (1H, m), 0.74 (3H, d, J=6Hz), 0.67 (3H,
31 d, J=6Hz), and 0.42 (3H, d, J=7Hz).

32 Δ_{C} (62.9MHz, D_6 -DMSO) 172.4, 171.6, 171.5, 148.9,
33 148.1, 137.9, 135.01, 34.9, 129.3, 128.1, 126.3, 123.5,
54.2, 46.6, 36.4, 25.4, 21.6, and 16.1.

1 Example 37

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
 4 alanine-N-[2-(3-aminopropyl)-pyridine]amide sodium
 5 salt.

6

7

8

9

10

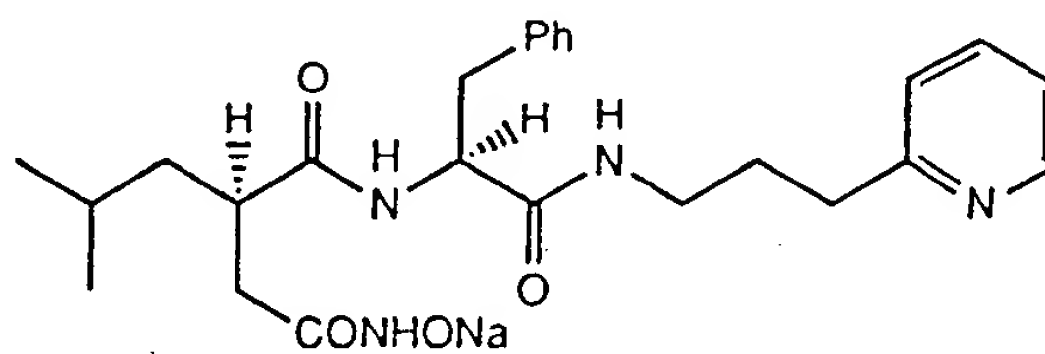
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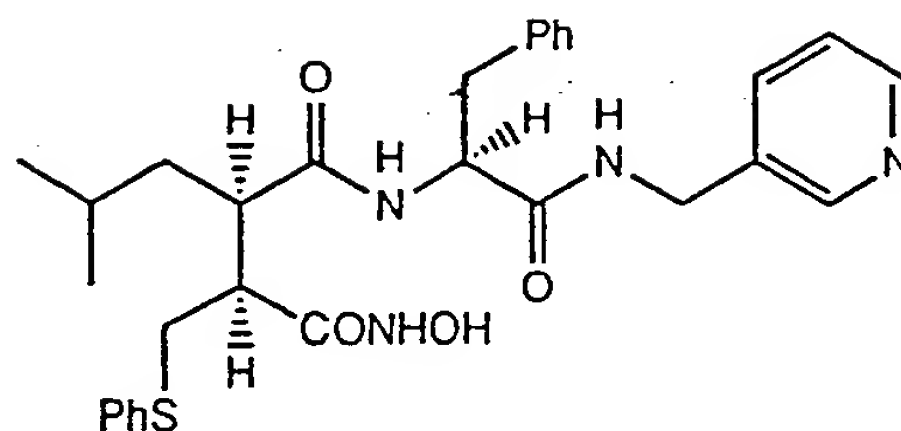
Prepared by the method described in Example 19 to give
 a compound with the following characteristics.

Delta_H (250MHz, D₆-DMSO) 0.68, (3H, d, J=6Hz), 0.76
 (3H, d, J=6Hz), 0.99 (1H, m), 1.34 (2H, m), 1.77, (2H,
 t, J=7Hz), 2.03 (2H, m), 2.65 (3H, m), 2.86 (1H, m),
 3.08 (3H, m), 4.44 (1H, m), 7.20 (7H, m), 7.49 (1H, dt,
 J=2,7Hz), 8.14 (1H, d, J=8Hz), and 8.47 (1H, d, J=4Hz).

Delta_C (62.9MHz, D₆-DMSO) 22.0, 23.4, 25.3, 29.0, 34.8,
 35.8, 37.41, 38.4, 40.6, 40.8, 54.2, 121.3, 122.9,
 126.3, 128.1, 129.2, 136.5, 149.1, 161.3, 167.7, 171.0,
 174.0, and 175.3.

30 Example 38

31 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)
 32 succinyl]-L-phenylalanine-N-(2-methylpyridyl) amide.
 33



a) 2R-Bromo-5-methylpentanoic acid.

D-Leucine (100g, 0.76 mol) and potassium bromide (317.5g, 2.67 mol) were dissolved in aqueous acid (150ml concentrated sulphuric acid in 500ml of water). The solution was cooled to just below 0° and sodium nitrite (69.6g, 0.95 mol in water) was added over 1h taking care to maintain the temperature between -1 and -2°. After addition was complete the mixture was kept at 0° for a further hour, then DCM was added and the mixture stirred for a few minutes. The layers were separated and the aqueous phase was washed with further portions of DCM (5 x 250ml). The combined organic layers were dried over magnesium sulphate then the solvent removed to give the acid as a pale yellow oil (123.1g, 0.63 mol, 83%)

$[\alpha]_D = +38.0^\circ$ (c = 2, methanol)

Δ_{H} (250 MHz, CDCl_3) 4.29 (1H, t, J = 6.5Hz, BrCHCO_2H), 1.91 (2H, t, J = 7Hz, CHCH_2CH), 1.83 (1H, m, Me_2CH), and 0.94 (6H, 2xd, J = 7Hz, $(\text{CH}_3)_2\text{CH}$)

b) tert-Butyl-2R-Bromo-5-methylpentanoate.

1 2R-Bromo-5-methylpentanoic acid (123g, 0.63 mol) was
2 dissolved in DCM (400ml) and the solution cooled to
3 -40° while isobutene was condensed in to roughly double
4 the volume. Maintaining the temperature at -40°
5 concentrated sulphuric acid (4ml) was added dropwise.
6 When the addition was complete the reaction was allowed
7 to warm to room temperature overnight. The resultant
8 solution was concentrate to half the volume by removing
9 the solvent at reduced pressure, then the DCM was
10 washed twice with an equal volume of 10% sodium
11 bicarbonate solution. The organic layer was dried over
12 magnesium sulphate and the solvent removed under
13 reduced pressure to leave the title compound as a
14 yellow oil (148.0g, 0.59 mol, 94%).

15
16 $[\alpha]_D = +23.0^{\circ}$ (c = 2, methanol)

17
18 Δ_H (250 MHz, $CDCl_3$) 4.18 (1H, t, J= 6.5Hz,
19 $BrCHCO_2H$), 1.89 (2H, m, $CHCH_2CH$), 1.78 (1H, m, Me_2CH),
20 1.49 (9H, s, $(CH_3)_3C$) and 0.94 (6H, 2xd, J= 7Hz,
21 $(CH_3)_2CH$)

22
23 Δ_C (63.9 MHz, $CDCl_3$) 167.0, 82.0, 46.3, 43.4, 27.6,
24 26.3, 22.2, and 21.6.

25
26 c) Benzyl (2-benzloxycarbonyl-3R-(tert-butoxy-
27 carbonyl)-5-methylhexanoate.

28
29 Dibenzyl malonate (124.5g, 0.44 mol) was taken up in
30 dry DMF and potassium tert-butoxide (49.2g, 0.44 mol)
31 was added portionwise with stirring and cooling. When
32 a homogeneous solution had formed it was cooled to 0°
33 then tert-butyl-2R-bromo-5-methylpentanoate (110.0g,

1 0.44 mol) in DMF (200 ml) was added dropwise over 1h.
2 When addition was complete the reaction was transferred
3 to a cold room at $<5^{\circ}$ and left for 4 days. The
4 reaction mixture was partitioned between ethyl acetate
5 and saturated ammonium chloride then the aqueous layer
6 extracted with further ethyl acetate (4x500ml), drying
7 and solvent removal left an oil (228g) heavily
8 contaminated with DMF. This oil was taken into ether (1
9 litre) and washed with brine (2x1l) then the organic
10 layer dried (magnesium sulphate), solvent removed to
11 leave the desired material (179g) contaminated with a
12 small amount of dibenzyl malonate.

13
14 $[\alpha]_D = +22.5^{\circ}$ (c = 2, methanol)
15

16 Δ_{H} (250 MHz, CDCl_3) 7.40 - 7.25 (10H, m, Aromatic
17 H), 5.14 (4H, 2xABq, CH_2Ph), 3.77 (1H, d, J= 13Hz,
18 $\text{BnO}_2\text{CCHCO}_2\text{Bn}$), 3.09 (1H, dt, J= 13,6Hz, $\text{CH}_2\text{CHCO}_2\text{tBu}$),
19 1.50 (3H, m, $\text{CH}_2 + \text{CHMe}_2$) 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$) and
20 0.88 (6H, 2xd, J= 7Hz).
21

22 d) [4 - Benzyloxy - 3 - benzyloxycarbonyl - 2R
23 -isobutylsuccinyl]- L-phenylalanine-N-(3-
24 aminomethylpyridine) amide
25

26 Benzyl(2-benzyloxycarbonyl-5-methyl-3R-tert-butoxy-
27 carbonyl)hexanoate (40g) was taken up in 5% water in
28 TFA (105 ml) and allowed to stand at 5° overnight.
29 After this time the TFA was evaporated under reduced
30 pressure then the residue partitioned between DCM
31 (250ml) and brine (50ml). Solvent removal left an oil
32 which crystallised on standing (30g).
33

1 The crude acid from this reaction was dissolved in DMF
2 (250ml), then HOBT (13.5g, 90 mmol), NMM (9.1g, 90mmol)
3 and phenylalanine-N-(3-aminomethylpyridine) amide (23g,
4 90mmol) were added at room temperature. The mixture
5 was cooled to 0° before dropwise addition of DCC
6 (18.5g, 90mmol) in THF (250ml). This solution was
7 stirred to room temperature over the weekend. The
8 precipitated DCU was removed by filtration then the
9 solvents were removed from the filtrate under reduced
10 pressure to leave an oil. This oily residue was
11 dissolved in ethyl acetate then washed with 10% citric
12 acid, 10% sodium bicarbonate and saturated brine. The
13 organic layer was dried (magnesium sulphate), filtered
14 then the solvent removed under reduced pressure to give
15 the title compound as an oil (73g). This material was
16 columned on silica using gradient elution (0 - 50%
17 ethyl acetate in hexane) to remove impurities and
18 separate a small amount of the minor diastereoisomer.
19 The material from the column (29.0g, 61%) was
20 recrystallised from ethanol/DIPE to give the title
21 compound as a white crystalline solid (17.1g)

22
23 e) [4-Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-phenyl-
24 alanine-N-(3-aminomethylpyridine) amide.

25
26 [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-
27 L-phenylalanine-N-(3-aminomethylpyridine) amide (5g,
28 7.9mmol) was taken up in ethanol, ammonium formate
29 (2.5g, 40mmol) added followed by 10% palladium on
30 charcoal (1g) as a slurry in isopropyl alcohol. After
31 30 minutes at room temperature the catalyst was removed
32 by filtration, then washed with ethanol to give a
33 solution of the crude diacid. To this was added

1 piperidine (1g) and the mixture stirred at room
2 temperature for 15 minutes before addition of aqueous
3 formaldehyde (40% solution, 5ml). After 18 hours at
4 room temperature the mixture was refluxed for 1 h.
5 Solvents were removed by rotary evaporation and the
6 residue partitioned between ethyl acetate and citric
7 acid. The acid layer was extracted with further
8 portions of ethyl acetate (2x250ml), the combined
9 organic layers were extracted with potassium carbonate
10 (3x200ml). These base extracts were acidified to pH 4
11 and re-extracted with DCM then the organic layer dried
12 over magnesium sulphate. Solvent removal under reduced
13 pressure gave the desired product as a white solid
14 (2.55g, 77%).

15
16 f) [4-Hydroxy-2R-isobutyl-3S-(phenylthiomethyl)-
17 succinyl]-L-phenylalanine-N-(3-aminomethylpyridine)
18 amide

19
20 [4-Hydroxy-2R-isobuty-3-ethenylsuccinyl]-L-phenyl-
21 alanine-N-(3-aminomethylpyridine) amide (1g, 2.4mmol)
22 was dissolved in thiophenol (10ml) and the mixture
23 stirred in the dark under nitrogen at 60° overnight.
24 Ether was added to the cooled reaction mixture and the
25 precipitated product collected by filtration. The
26 solid was washed with large volumes of ether and dried
27 under vacuum to give the title compound (650mg, 51%).

28
29 g) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthio-
30 methyl)succinyl]-L-phenylalanine-N-(3-aminomethyl-
31 pyridine) amide

32
33 [4-Hydroxy-2R-isobutyl-3S-phenylthiomethyl succinyl]-L-

1 phenylalanine-N-(2-methylpyridyl) amide (0.2g, 0.4
2 mmol) and HOBT (0.07g, 0.5 mmol) were dissolved in 1:1
3 DCM/DMF and the mixture cooled to 0°C before adding
4 WSDCI (0.09g, 0.5mmol) and NMM (0.05g, 0.5mmol). The
5 mixture was stirred at 0°C for 1h to ensure complete
6 formation of the activated ester. Hydroxylamine
7 hydrochloride (0.04g, 0.6mmol) and NMM (0.06g, 0.6mmol)
8 were dissolved in DMF then this mixture was added
9 dropwise to the cooled solution of the activated ester.
10 After 1h the reaction was poured into ether/water (1:1)
11 whereupon the desired product precipitated as white
12 crystals. These were collected by filtration, further
13 washed with ether and water, then dried under vacuum at
14 50°C. This material was recrystallised from
15 methanol/water (1:1) to remove a trace of the minor
16 diastereomer (0.1g, 0.2mmol, 48%).

17

18 m.p. 207°C

19

20 $[\alpha]_D = -63^\circ$ (c=1, methanol)

21

22 Analysis calculated for $C_{30}H_{36}N_4O_5S$

23 Requires: C65.67 H6.61 N10.21

24 Found: C65.72 H6.71 N10.02

25

26 δ_H (250MHz, D_6 -DMSO) 8.84 (1H, s, $NHOH$), 8.57 -
27 8.41 (3H, d, $CONH$ and aromatic H), 7.57 (1H, d, J =
28 6Hz, $CONHMe$), 7.45 - 6.96 (7H, m, aromatic H), 4.71
29 (1H, m, $CHCH_2Ph$), 4.30 (2H, m, $CH_2C_6H_5N$), 2.98 (1H,
30 dd, J = 14,4Hz, $CHCH_2Ph$), 2.82 (1H, dd, J = 14,10Hz,
31 $CHCH_2Ph$), 2.50 (2H, m), 2.17 (2H, m), 1.33 (2H, m,
32 $CHCH_2(CH_3)_2$), 0.85 (1H, m, $CH_2CH(CH_3)_2$), 0.77 (3H, d,
33 J = 6Hz, $CH(CH_3)_2$), and 0.70 (3H, d, J = 6Hz, $CH(CH_3)_2$).

1 Example 39

2

3 **Collagenase inhibition activity**

4

5 The potency of compounds of general formula I to act
6 as inhibitors of collagenase (a metalloproteas
7 involved in tissue degradation) was determined by the
8 procedure of Cawston and Barrett, (Anal. Biochem., 99,
9 340-345, 1979), hereby incorporated by reference,
10 whereby a 1mM solution of the inhibitor being tested or
11 dilutions thereof was incubated at 37° for 16 hours
12 with collagen and collagenase (buffered with 25mM
13 Hepes, pH 7.5 containing 5mM CaCl₂, 0.05% Brij 35 and
14 0.02% NaN₃). The collagen was acetylated ¹⁴C collagen
15 prepared by the method of Cawston and Murphy (Methods
16 in Enzymology, 80, 711, 1981), hereby incorporated by
17 reference. The samples were centrifuged to sediment
18 undigested collagen and an aliquot of the radioactive
19 supernatant removed for assay on a scintillation
20 counter as a measure of hydrolysis. The collagenase
21 activity in the presence of 1 mM inhibitor, or a
22 dilution thereof, was compared to activity in a control
23 devoid of inhibitor and the results reported below as
24 that inhibitor concentration effecting 50% inhibition
25 of the collagenase (IC₅₀).

26

27 Compound of Example No.IC₅₀

28

3

70 nM

29

6

20 nM

30

11

15 nM

31

32

33

1 Example 40

2

3 **Stromelysin inhibition activity**

4

5 The potency of compounds of general formula I to act as
6 inhibitors of stromelysin was determined using the
7 procedure of Cawston et al (Biochem. J., 195, 159-165
8 1981), hereby incorporated by reference, whereby a 1mM
9 solution of the inhibitor being tested or dilutions
10 thereof was incubated at 37°C for 16 hours with
11 stromelysin and ¹⁴C acetylate casein (buffered with
12 25mM Hepes, pH 7.5 containing 5mM CaCl₂, 0.05% Brij 35
13 and 0.02% NaN₃. The casein was ¹⁴C acetylated
14 according to the method described in Cawston et al
15 (Biochem. J., 195, 159-165, 1981), hereby incorporated
16 by reference. The stromelysin activity in the presence
17 of 1mM, or a dilution thereof, was compared to activity
18 in a control devoid of inhibitor and the results
19 reported below as that inhibitor concentration
20 effecting 50% inhibition of the stromelysin (IC₅₀).

21

22 Compound of Example No.IC₅₀

23

11

50 nM

24

25 Examples of unit dosage compositions are as follows:

26

27

28

29

30

31

32

33

1 Example 41

2

3 **Capsules:**

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32

33

Per 10,000

IngredientsPer CapsuleCapsules

1. Active ingredient

(Cpd of Formula I) 40.0 mg

400 g

2. Lactose 150.0 mg

1500 g

3. Magnesium

stearate 4.0 mg

40 g

194.0 mg

1940 g

Procedure for capsules:

Step 1. Blend ingredients No. 1 and No. 2 in a suitable blender.

Step 2. Pass blend from Step 1 through a No. 30 mesh (0.59 mm) screen.

Step 3. Place screened blend from Step 2 in a suitable blender with ingredient No. 3 and blend until the mixture is lubricated.

Step 4. Fill into No. 1 hard gelatin capsule shells on a capsule machine.

1 Example 42

2

3 **Tablets:**

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

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21

22

23

24

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26

27

28

29

30

31

32

33

Per 10,000

IngredientsPer TabletTablets

1. Active ingredient

(Cpd of Form. I) 40.0 mg

400 g

2. Corn Starch 20.0 mg

200 g

3. Alginic acid 20.0 mg

200 g

4. Sodium alginate 20.0 mg

200 g

5. Magnesium

stearate

1.3 mg13 g

101.3 mg

1013 g

Procedure for tablets:

Step 1. Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2. Add sufficient water portionwise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38) screen.

Step 4. The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5. The dry granules are lubricated with ingredient No. 5.

Step 6. The lubricated granules are compressed on a suitable tablet press.

1 Example 43

2

3 **Intramuscular Injection:**

4	<u>Ingredient</u>	<u>Per ml.</u>	<u>Per liter</u>
5	1. Formula I compound		
6	Active ingredient	10.0 mg	10 g
7	2. Istonic buffer		
8	solution pH 4.0.	q.s.	q.s.

9

10 **Procedure:**

11 Step 1. Dissolve the active ingredient in the buffer
12 solution.

13 Step 2. Aseptically filter the solution from Step 1.

14 Step 3. The sterile solution is now aseptically
15 filled into sterile ampoules.

16 Step 4. The ampoules are sealed under aspetic
17 conditions.

18

19 Example 44

20

21 **Suppositories:**

22			Per
23	<u>Ingredients</u>	<u>Per Supp.</u>	<u>1,000 Supp</u>
24	1. Formula I compound		
25	Active ingredient	40.0 mg	40 g
26	2. Polyethylene Glycol		
27	1000	1350.0 mg	1,350 g
28	3. Polyethylene Glycol		
29	4000	<u>450.0 mg</u>	<u>450 g</u>
30		1840.0 mg	1,840 g

31

32

33

1 Procedure:

2 Step 1. Melt ingredient No. 2 and No. 3 together and
3 stir until uniform.

4 Step 2. Dissolve ingredient No. 1 in the molten mass
5 from Step 1 and stir until uniform.

6 Step 3. Pour the molten mass from Step 2 into
7 suppository moulds and chill.

8 Step 4. Remove the suppositories from moulds and
9 wrap.

10

11 Example 45

12

13 Eye Ointment

14

15 An appropriate amount of a compound of general formula
16 I is formulated into an eye ointment base having the
17 following composition:

18

19	Liquid paraffin	10%
20	Wool fat	10%
21	Yellow soft paraffin	80%

22

23 Example 46

24

25 Topical skin ointment

26

27 An appropriate amount of a compound of general formula
28 I is formulated into a topical skin ointment base
29 having the following composition:

30

31	Emulsifying wax	30%
32	White soft paraffin	50%
33	Liquid paraffin	20%

1 CLAIMS

2

3 1. A compound of general formula I:

4

5

6

7

8

9

10

11 wherein:

12

13 R^1

14

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26

27 R^2

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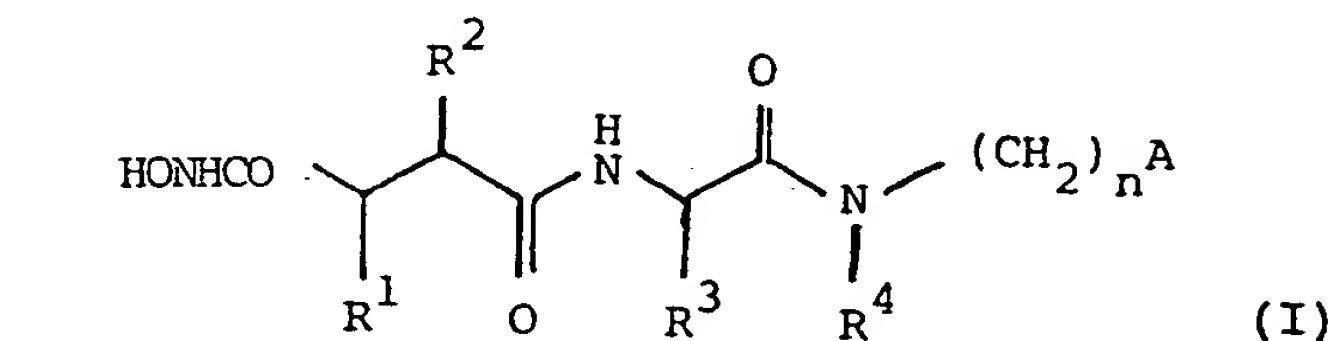
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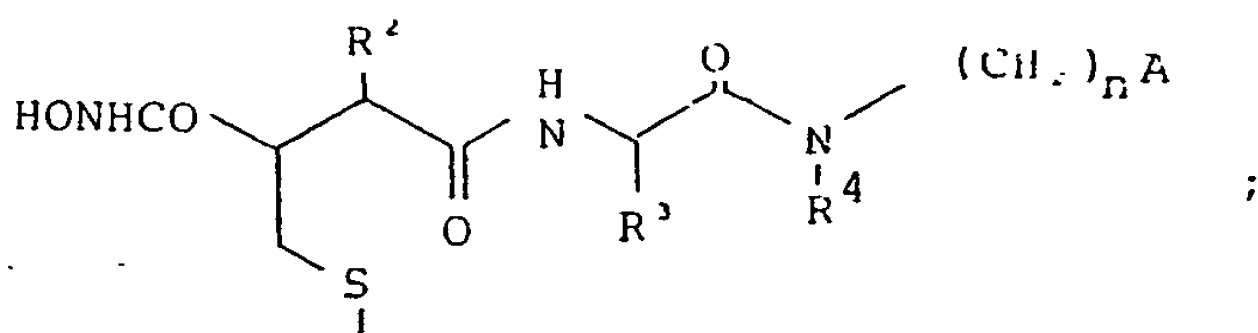
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32

33



represents a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkenyl, phenyl, phenyl($\text{C}_1\text{-C}_6$)alkyl, $\text{C}_1\text{-C}_6$ alkylthiomethyl, phenylthiomethyl, substituted phenylthiomethyl, phenyl($\text{C}_1\text{-C}_6$)alkylthiomethyl or heterocyclylthiomethyl group; or R^1 represents $-\text{SR}^x$ wherein R^x represents a group



represents a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkenyl, phenyl($\text{C}_1\text{-C}_6$)alkyl, cycloalkyl($\text{C}_1\text{-C}_6$)alkyl, or cycloalkenyl($\text{C}_1\text{-C}_6$)alkyl;

1 R^3 represents an amino acid side chain or a C_1-C_6
2 alkyl, benzyl, (C_1-C_6) alkoxybenzyl;
3 benzyloxy (C_1-C_6) alkyl or benzyloxy benzyl group;

4
5 R^4 represents a hydrogen atom or a methyl group;

6
7 n is an integer from 1 to 6; and

8
9 A represents the group $-NH_2$, a substituted acyclic
10 amine or a heterocyclic base;

11
12 or a salt and/or N-oxide and/or (where the compound is
13 a thio-compound) a sulphoxide or sulphone thereof.

14
15 2. A compound as claimed in claim 1, in which the
16 chiral centre adjacent the substituent R^3 has S
17 stereochemistry.

18
19 3. A compound as claimed in Claim 1 or 2, wherein R^1
20 represents a hydrogen atom or a C_1-C_4 alkyl,
21 phenylthiomethyl or heterocyclylthiomethyl group.

22
23 4. A compound as claimed in Claim 1, 2 or 3, wherein
24 R^2 represents a C_3-C_6 alkyl group.

25
26 5. A compound as claimed in any one of Claims 1 to 4,
27 wherein R^3 represents a benzyl,
28 4- (C_1-C_6) alkoxyphenylmethyl or benzyloxy benzyl group.

29
30 6. A compound as claimed in any one of Claims 1 to 5,
31 wherein R^4 represents a hydrogen atom.

32

33

- 1 7. A compound as claimed in any one of Claims 1 to 6,
2 wherein n has the value 1, 2 or 3.
3
- 4 8. A compound as claimed in any one of Claims 1 to 7,
5 wherein A represents a morpholinyl, piperidinyl, 2-, 3-
6 or 4-pyridyl or pyrrolidinyl group.
7
- 8 9. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
9 alanine-N-[(2-aminoethyl)-2(RS)-(1-methylpyrrolidine)]-
10 amide,
11
- 12 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
13 alanine-N-[1-(2-aminoethyl)-piperidine]amide,
14
- 15 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
16 alanine-N-[1-(2-aminoethyl)-pyrrolidine]amide,
17
- 18 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
19 alanine-N-[1-(3-aminopropyl)-2(RS)-methylpiperidine]-
20 amide,
21
- 22 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
23 alanine-N-[2-(2-aminoethyl)-1-methylpyrrole]amide,
24
- 25 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
26 alanine-N-(3-aminomethylpyridine)amide,
27
- 28 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
29 alanine-N-(2-aminomethylpyridine)amide,
30
- 31 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
32 alanine-N-(4-aminomethylpyridine)amide,
33

- 1 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
- 2 alanine-N-(1-(3-aminopropyl)-imidazole)amide,
- 3
- 4 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
- 5 alanine-N-(2-aminomethylbenzimidazole)amide,
- 6
- 7 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
- 8 phenylalanine-N-[4-(2-aminoethyl)-morpholino]amide,
- 9
- 10 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
- 11 alanine-N-[4-(2-aminoethyl)-morpholine]amide,
- 12
- 13 [4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-phenyl-
- 14 alanine-N-[2-(2-aminoethyl)-pyridine]amide,
- 15
- 16 [4-(N-Hydroxyamino)-2(R,S)-isobutylsuccinyl]-L-phenyl-
- 17 alanine-N-[4-(2-aminopropyl)-morpholine]amide,
- 18
- 19 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
- 20 alanine-N-(3-aminomethylpyridine)amide hydrochloride,
- 21
- 22 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
- 23 alanine-N-[4-(2-aminoethyl)-morpholine]amide
- 24 hydrochloride,
- 25
- 26 [4-(N-Hydroxyamino)-2(RS)-isobutylsuccinyl]-L-phenyl-
- 27 alanine-N-(4-aminomethylpyridine)amide hydrochloride,
- 28
- 29 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
- 30 phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide
- 31 hydrochloride or
- 32
- 33

- 1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
- 2 phenylalanine-N-[4-(2-aminoethyl)-morpholine]amide
- 3 sodium salt,
- 4
- 5 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
- 6 alanine-N-[1-(3-aminopropyl)-imidazole]amide
- 7
- 8 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
- 9 alanine-N-[2-(3-aminopropyl)-pyridine]amide
- 10
- 11 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
- 12 alanine-N-[2-aminoethyl)-N,N-diethylamine]amide
- 13
- 14 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 15 l-phenylalanine-N-[3-aminomethyl-pyridine]amide
- 16
- 17 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 18 l-phenylalanine-N-[4-aminomethyl-pyridine]amide
- 19
- 20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 21 l-phenylalanine-N-[2-aminomethyl-pyridine]amide
- 22
- 23 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 24 l-phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide
- 25
- 26 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
- 27 alanine-N-[2-(2-aminoethyl)-pyridine]amide hydro-
- 28 chloride
- 29
- 30 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-l-phenyl-
- 31 alanine-N-[4-aminomethyl-pyridine]amide hydrochloride
- 32
- 33

- 1 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-1-phenyl-
- 2 alanine-N-[2-aminomethyl-pyridine]amide hydrochloride
- 3
- 4 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-1-phenyl-
- 5 alanine-N-[2-(3-aminopropyl)-pyridine]amide hydro-
- 6 chloride
- 7
- 8 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 9 1-phenylalanine-N-[3-aminomethyl-pyridine]amide hydro-
- 10 chloride
- 11
- 12 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 13 1-phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide
- 14 hydrochloride
- 15
- 16 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 17 1-phenylalanine-N-[2-aminomethyl-pyridine]amide
- 18 hydrochloride
- 19
- 20 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 21 1-phenylalanine-N-[4-aminomethyl-pyridine]amide sodium
- 22 salt
- 23
- 24 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 25 1-phenylalanine-N-[2-(2-aminoethyl)-pyridine]amide
- 26 sodium salt
- 27
- 28 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
- 29 1-phenylalanine-N-[3-aminomethyl-pyridine]amide sodium
- 30 salt
- 31
- 32 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-1-phenyl-
- 33 alanine-N-[2-(3-aminopropyl)-pyridine]amide sodium salt

1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)
2 succinyl]-L-phenylalanine-N-(2-methylpyridyl) amide

3
4 or the free base, free acid or salt thereof, where
5 appropriate.

6
7 10. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
8 alanine-N-(3-aminomethylpyridine)amide or

9
10 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-p-
11 henylalanine-N-[4-(2-aminoethyl)-morpholino]amide,

12
13 or a salt thereof.

14
15 11. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
16 alanine-N-(3-aminomethylpyridine)amide or a salt
17 thereof.

18
19 12. A compound as claimed in any one of claims 1 to 11
20 for use in human or veterinary medicine.

21
22 13. The use of a compound as claimed in any one of
23 claims 1 to 11 in the preparation of an agent for use
24 in the management of disease involving tissue
25 degradation and/or in the promotion of wound healing.

26
27 14. A pharmaceutical or veterinary formulation
28 comprising a compound as claimed in any one of claims 1
29 to 11 and a pharmaceutically and/or veterinarily
30 acceptable carrier.

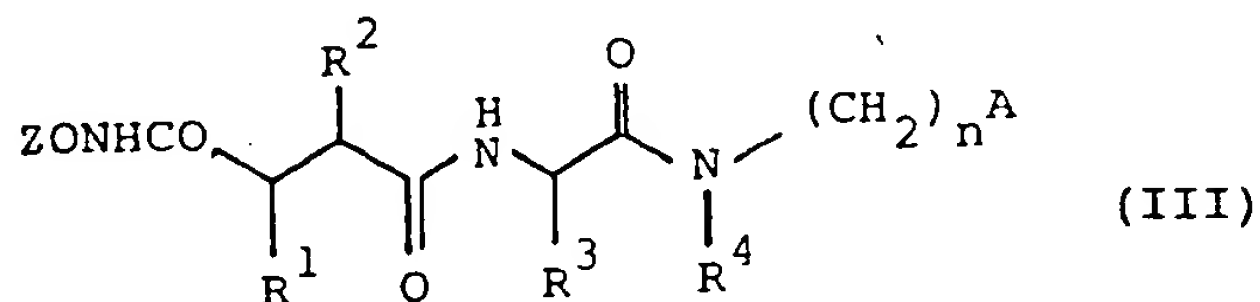
31

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33

1 15. A process for preparing a compound of general
 2 formula I as defined in claim 1, the process
 3 comprising:

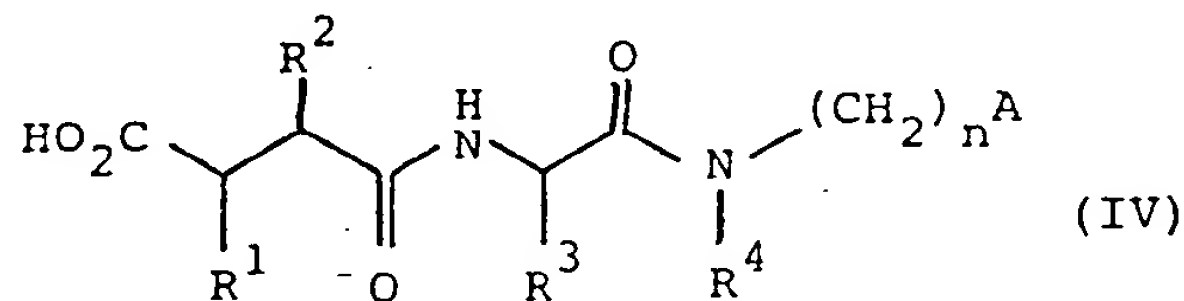
4
 5 (a) deprotecting a compound of general formula III



11 wherein:

12
 13 R^1 , R^2 , R^3 , R^4 , n and A are as defined in general
 14 formula I and Z represents a protective group; or

15
 16 (b) reacting a compound of general formula IV



22 wherein:

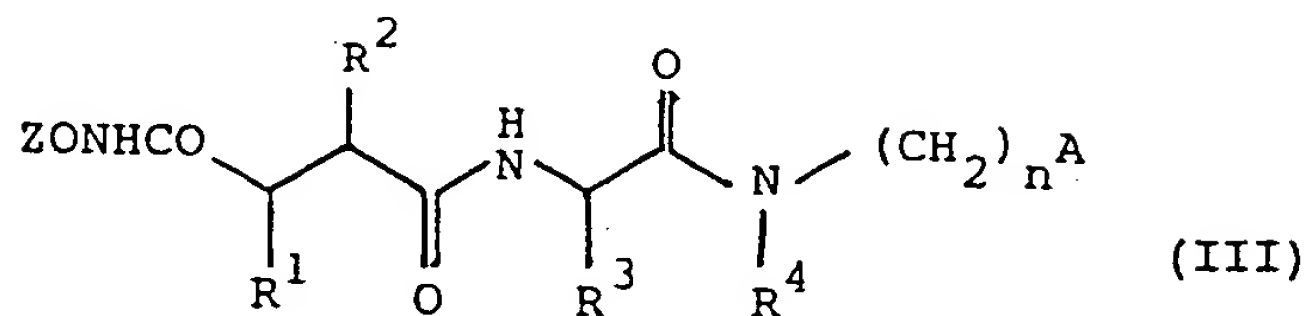
23
 24 R^1 , R^2 , R^3 , R^4 , n and A are as defined in general
 25 formula I, with the proviso that R^1 represents a
 26 hydrogen atom,

27
 28 with hydroxylamine or a salt thereof; and

29
 30 (c) optionally after step (a) or step (b) converting a
 31 compound of general formula I into another compound of
 32 general formula I.

33

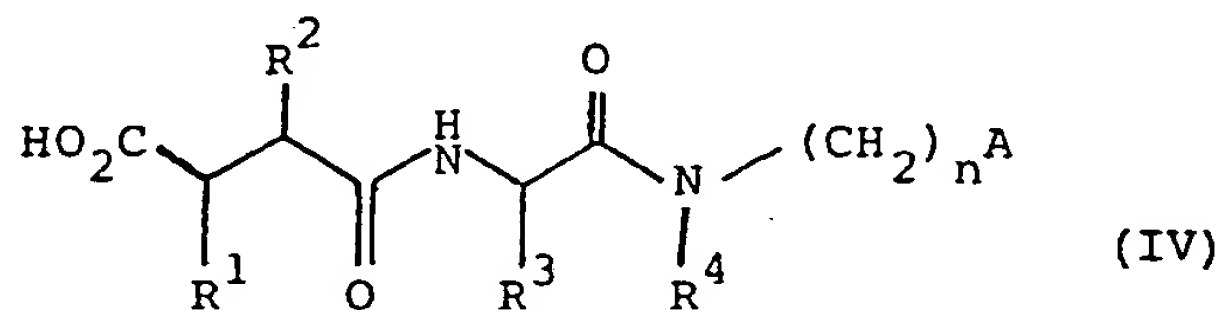
1 16. A compound of general formula III



7 wherein:

9 R¹, R², R³, R⁴, n and A are as defined in general
 10 formula I and Z represents a protective group; or

12 17. A compound of general formula IV



18 wherein:

20 R¹, R², R³, R⁴, n and A are as defined in general
 21 formula I, with the proviso that R¹ represents a
 22 hydrogen atom.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/01398

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
C 07 C 259/06, C 07 D 207/335, 213/40, 211/26, 207/08, IPC: 235/14, 233/61, 295/12, A 61 K 31/395, 31/13		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC ⁵	C 07 C 259/00, C 07 D 207/00, 211/00, 213/00, 233/00, 235/00, 295/00, 521/00	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A, 0236872 (F. HOFFMANN-LA ROCHE AG) 16 September 1987, see claim 1 (cited in the application) --	1-16
A	EP, A, 0012401 (MERCK & CO, INC.) 25 June 1980, see claim 1 (cited in the application) --	1-16
A	DE, A, 2720996 (E.R. SQUIBB & SONS) 24 November 1977, see claim 1 & US, A, 4105789 (cited in the application) --	1-16
A	EP, A, 0274453 (LABORATOIRE ROGER BELLON) 13 July 1988, see claim 1 --	1-16
A	EP, A, 0214639 (G.D. SEARLE & CO.) 18 March 1987, see claim 1 & US, A, 4599361 (cited in the application) --	1-16
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
8th March 1990	12. 04. 90	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	T.K. WILLIS	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	<p>Chemical Abstracts, vol. 83, no. 21, 24 November 1975, (Columbus, Ohio, US), C.F.Hayward et al.: "Effect of reversal of the direction of peptide bonds on the interaction between peptide hormones and receptors", see page 625, abstract 179553w & Pept. Proc. Eur. Pept. Symp. 13th 1974, (publ. 1975), 287-98</p> <p>& Questel Generic DARC on-line graphics of compound nos 57022-75-0 and 57022-77-2</p> <p>-----</p>	17

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 8901398
SA 32977

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 03/04/90
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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